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Preface

There is an old joke with a well-known punch line about a man who has just fallen from the 86th floor of the Empire State Building in New York. As he passes the 30th floor, he is heard saying to himself 'so far, so good'...

Most of us laugh because we know where the man is headed, and that he must know too. But, our laughter usually has a guilty edge. We know that many of us are guilty of occasionally displaying a 'so far, so good' attitude in our own lives. We think of the smoker who says that about the possibility of getting lung cancer or heart disease and who counts on beating the odds because he feels healthy at the moment. That smoker will not find out if he won the bet until many years later, and by then it is often too late. The 'so far, so good' attitude to health is so common that people even kid themselves about it. One smoker told me that smoking would only cut a few years off his life, and that he did not mind losing the last few years because they are usually not much fun anyway.

Unlike the optimist in the joke, whose end is virtually certain, many of us live like the smoker, playing the odds and reassuring ourselves 'so far, so good'. Diseases like cancer usually take many years to develop, and we try not to think how some of the things we do casually can affect the long-term odds by compromising the natural processes that protect us. We rely on our bodies to be strong and resilient all the time. Yet, we know there are limits to the body's natural ability to reverse damage to cells. We also know that there may be gaps in the ability of our genetic endowment to cope with damage. At some level, we all know it is just common sense to try to minimize damage to our bodies and maximize the ability to repair.

These opening paragraphs provide a quick introduction to the theme of this issue of Pathophysiology and a summary of the point of view of its authors. The public is currently interested in possible hazards from radio frequency (RF) due to cellphones, towers, WiFi, etc. The concern is certainly warranted, but we are surrounded by electromagnetic fields (EMFs) of many frequencies, and there are also significant biological effects and known risks from low frequency EMF. The scientific problem is to determine the nature of EMF interaction with biological systems and develop ways of coping with harmful effects in all frequency ranges, as well as their cumulative effects. The practical problem is to minimize the harmful biological effects of all EMF.

The technical papers in this issue are devoted to an examination and an evaluation of evidence gathered by scientists regarding the effects of EMF, especially RF radiation, on living cells and on the health of human populations. The laboratory studies point to significant interactions of both power frequency and RF with cellular components, especially DNA. The epidemiological studies point to increased risk of developing certain cancers associated with long-term exposure to RF. Overall, the scientific evidence shows that the risk to health is significant, and that to deny it is like being in free-fall and thinking 'so far, so good'. We must recognize that there is a potential health problem, and that we must begin to deal with it responsibly as individuals and as a society.

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EMF effects on DNA

M. Blank and R. Goodman (USA): Electromagnetic Fields Stress Living Cells

Exhibit A

Abbreviations: EMF, electromagnetic fields; Hz, hertz (cycles/s the unit of frequency); ELF, extremely low frequency ($3–3 \times 10^3$ Hz) power frequency is 50–60 Hz; RF, radio frequency (band width 3×10^3 to 3×10^{11} Hz); UHF, ultrahigh frequency band the RF sub-division used for cell phones (3×10^8 to 3×10^9 Hz).

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J.L. Phillips, N.P. Singh and H. Lai (USA): Electromagnetic Fields and DNA damage

H.W. Rűdiger (Austria): Genotoxic effects of electromagnetic exposure in vitro

EMF effects on the brain

H. Nittby, A. Brun, J. Eberhardt, L. Malmgren, B.R.R. Persson and L.G. Salford (Sweden): Increased blood–brain barrier permeability in mammalian brain seven days after exposure to the radiation from a GSM-900 mobile phone

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O. Johansson: Disturbance of the immune system by electromagnetic fields: A potentially underlying cause for cellular damage and tissue repair reduction which could lead to disease and impairment disturbance

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C. Sage and D.O. Carpenter: Public Health Implications of Wireless Technologies

Special Issue on EMF

Bioelectromagnetics, the study of biological effects of electromagnetic fields (EMF), is an interdisciplinary science with a technical literature that is not easily accessible to the non-specialist. To increase access of the public to the technical literature and to the health implications of the scientific findings, the Bioinitiative Report was organized by an international group of scientists and published online at www.bioinitiative.org on August 31, 2007. The report has been widely read, and was cited in September 2008 by the European Parliament when it voted overwhelmingly that the current EMF safety standards were obsolete and needed to be reviewed.

This special issue of Pathophysiology includes scientific papers on the EMF issue by contributors to the Bioiniative Report, as well as others, and is prepared for scientists who are not specialists in bioelectromagnetics. Each paper is independent and self-contained. To help the reader appreciate how the different subjects contribute to an understanding of the EMF issue, the papers are arranged in groups that emphasize key areas, and the role of science in analyzing the problem and evaluating possible solutions. The subject headings are:

- DNA to show biological effects at the sub-cellular level that occur at very low EMF thresholds and across frequency ranges of the EM spectrum. Interactions with DNA may account for many of the effects of EMF, and they raise the possibility that genetic damage due to EMF can lead to cancer.
- The Brain is exposed to radiation from mobile phone antennas, and laboratory studies show that the radiation causes leakage of the protective blood–brain barrier, as well as the death of neurons in the brain. Radiation emitted from base stations can affect all who are in the vicinity. Epidemiological studies have shown a relation between exposure to mobile phones, base-stations and the development of brain tumors. Some epidemiological studies have significant flaws in design, and the risk of brain cancer may be greater than reported in the published results.
- In addition to the risk of brain cancer, EMF in the environment may contribute to diseases like Alzheimer's dementia and breast cancer in humans, as well as reproductive and developmental effects in animals in the wild. EMF affect the biochemical pathways and immunological mechanisms that link the different organ systems in our bodies and those of animals. The human body can act as an antenna for RF signals, and a small percentage of the population appears to be so sensitive to EMF that it interferes with their daily lives. In addition to the growing presence of EMF signals in the environment, the complexity of the signals may be important in altering biological responses. These are among the many factors that must be considered in approaching EMF safety issues.
- Science as a guide to public policy

Four centuries ago, when Francis Bacon envisioned a course for modern science, he expressed the idea that *knowledge is power that should be applied for the benefit of mankind*. It is in keeping with that ethical standard that the last two papers in this issue show how knowledge gained from scientific research can help solve problems arising from EMF in our environment. The first of these papers discusses the Precautionary Principle, its growing acceptance as a rational approach to environmental issues, and how past experience can help us deal with the EMF issue. The second paper, by the editors of the original BioInitiative Report, is an update on how best to deal with the challenge of EMF in the environ-

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ment and, specifically, the problems accompanying wireless technologies.

We trust that the reviews and original research papers will increase awareness of the growing impact of EMF in the environment, and the need for modern society to deal expeditiously with the potential health problems brought to light by EMF research.

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Electromagnetic fields stress living cells

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Abstract

Electromagnetic fields (EMF), in both ELF (extremely low frequency) and radio frequency (RF) ranges, activate the cellular stress response, a protective mechanism that induces the expression of stress response genes, e.g., HSP70, and increased levels of stress proteins, e.g., hsp70. The 20 different stress protein families are evolutionarily conserved and act as 'chaperones' in the cell when they 'help' repair and refold damaged proteins and transport them across cell membranes. Induction of the stress response involves activation of DNA, and despite the large difference in energy between ELF and RF, the same cellular pathways respond in both frequency ranges. Specific DNA sequences on the promoter of the HSP70 stress gene are responsive to EMF, and studies with model biochemical systems suggest that EMF could interact directly with electrons in DNA. While low energy EMF interacts with DNA to induce the stress response, increasing EMF energy in the RF range can lead to breaks in DNA strands. It is clear that in order to protect living cells, EMF safety limits must be changed from the current thermal standard, based on energy, to one based on biological responses that occur long before the threshold for thermal changes.
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Keywords: DNA; Biosynthesis; Electromagnetic fields; ELF; RF

1. Electromagnetic fields (EMF) alter protein synthesis

Until recently, genetic information stored in DNA was considered essentially invulnerable to change as it was passed on from parent to progeny. Mutations, such as those caused by cosmic radiation at the most energetic end of the EM spectrum, were thought to be relatively infrequent. The model of gene regulation was believed to be that the negatively charged DNA was tightly wrapped up in the nucleus with positively charged histones, and that most genes were 'turned off' most of the time. Of course, different regions of the DNA code are being read more or less all the time to replenish essential proteins that have broken down and those needed during cell division.

New insights into the structure and function of DNA have resulted from numerous, well-done laboratory studies. The demonstration that EMF induces gene expression and the synthesis of specific proteins [1,2] generated considerable controversy from power companies, government agencies, physicists, and most recently, cell phone companies. Physicists have insisted that the reported results were not possible because there was not enough energy in the power frequency range (ELF) to activate DNA. They were thinking solely of mechanical interaction with a large molecule and not of the large hydration energy tied up in protein and DNA structures that could be released by small changes in charge [3]. Of the biologists who accepted such results [4], most thought that the EMF interaction originated at, and was amplified by, the cell membrane and not with DNA.

It is now generally accepted that weak EMF in the power frequency range can activate DNA to synthesize proteins. An EMF reactive sequence in the DNA has been identified [5] and shown to be transferable to other gene promoters [6]. This DNA sequence acts as an EMF sensitive antenna

Abbreviations: EMF, electromagnetic fields; Hz, hertz; ELF, extremely low frequency; RF, radio frequency; MAPK, mitogen activated protein kinase; ERK1\2, extracellular signal regulated kinase; JNK, c-Jun-terminal kinase p38MAPK; SAPK, stress activated protein kinase; NADH, nicotinamide adenine dinucleotide dehydrogenase; ROS, reactive oxygen species.

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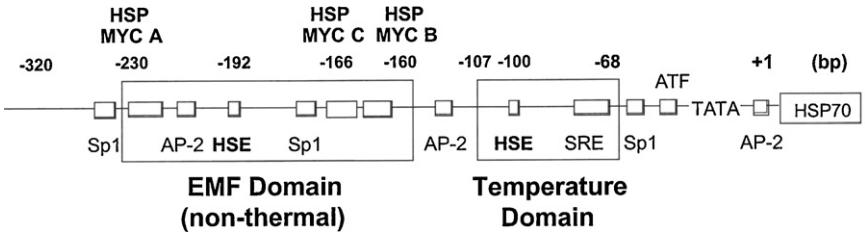

Fig. 1. Diagram of the HSP70 promoter showing the two different DNA sequences that have been identified as activated by EMF (non-thermal) and by thermal stimuli, respectively. The EMF domain contains three nCTCTn consensus sequences (electromagnetic response elements; EMRE), and differs from the consensus sequence (nGAAn) in the temperature or thermal domain.

that responds to EMF when transfected into reporter genes. Research at the more energetic levels of power frequency [7] and in the RF [8] ranges has shown that exposure to EMF can lead to breaks in the DNA strands. Therefore, DNA can no longer be considered unaffected by environmental EMF levels. It can be activated and damaged by EMF at levels that are considered safe [9]. The vulnerability of DNA to environmental influences and the possible dangers associated with EMF, had been underscored by discovery of EMF activation of the cellular stress response in the ELF range [10,11]. The cellular stress response is an unambiguous signal by the cell that EMF is potentially harmful.

2. Physiological stress and cellular stress

Discussions of physiological stress mechanisms usually describe responses of the body to pain, fear, 'oxygen debt' from muscle overexertion. These responses are mediated by organ systems. For example, the nervous system transmits action potentials along a network of nerves to cells, such as adrenal glands, that release rapidly acting agents such as epinephrine and norepinephrine and slower acting mineralocorticoids. These hormones are transported throughout the body by the circulatory system. They mobilize the defenses to cope with the adverse conditions and enable the body to 'fight or flee' from the noxious stimuli. The defensive actions include changes in heart rate, breathing rate, muscle activity, etc.

In addition to the responses of organ systems, there are protective mechanisms at the cellular level known as the cellular stress response. These mechanisms are activated by damage to cellular components such as DNA and protein [12], and the responses are characterized by increased levels of stress proteins [13] indicating that stress response genes have been upregulated in response to the stress.

The first stress response mechanism identified was the cellular reaction to sharp increases in temperature [14] and was referred to as 'heat shock', a term that is still retained in the nomenclature of the protective proteins, the hsps, heat shock proteins. Stress proteins are designated by the prefix 'hsp' followed by a number that gives the molecular weight in kilodaltons. There are about 20 different protein families ranging in molecular weight from a few kilodaltons to over 100 kD, with major groups of proteins around 30 kD, 70 kD and 90 kD.

Research on the 'heat shock' response has shown that hsp synthesis is activated by a variety of stresses that are potentially harmful to cells, including physical stimuli like pH and osmotic pressure changes, as well as chemicals such as alcohol and toxic metal ions like Cd^{2+}. EMF is a recent addition to the list of physical stimuli. It was initially shown in the power frequency (extremely low frequency, ELF) range [13], but shortly afterwards, radio frequency (RF) fields [15] and amplitude modulated RF fields [16] were shown to activate the same stress response.

Studies of stress protein stimulation by low frequency EMF have focused on a specific DNA sequence in the gene promoter that codes for hsp70, a major stress protein. Synthesis of this stress protein is initiated in a region of the promoter (see Fig. 1) where a transcription factor known as heat shock factor 1 (HSF-1) binds to a heat shock element (HSE). This EMF sensitive region on the HSP70 promoter is upstream from the thermal domain of the promoter and is not sensitive to increased temperature. The binding of HSF-1 to HSE occurs at −192 in the HSP70 promoter relative to the transcription initiation site. The EMF domain contains three nCTCTn myc-binding sites −230, −166 and −160 relative to the transcription initiation site and upstream of the binding sites for the heat shock (nGAAn) and serum responsive elements [5,6,17,18]. The electromagnetic response elements (EMREs) have also been identified on the c-*myc* promoter and are also responsive to EMF. The sensitivity of the DNA sequences, nCTCTn, to EMF exposures has been demonstrated by transfecting these sequences into CAT and Luciferase reporter genes [6]. Thus, the HSP70 promoter contains different DNA regions that are specifically sensitive to different stressors, thermal and non-thermal.

Induction of increased levels of the major stress protein, hsp70, by EMF is rapid, within 5 min. Also it occurs at extremely low levels of energy input, 14 orders of magnitude lower than with a thermal stimulus [10]. The far greater sensitivity to EMF than to temperature change in elevating the protective protein, hsp70, has been demonstrated to have potential clinical application, preventing injury from ischemia reperfusion [19–21]. George et al. [22] have shown the non-invasive use of EMF-induced stress proteins improved hemodynamic parameters during reperfusion

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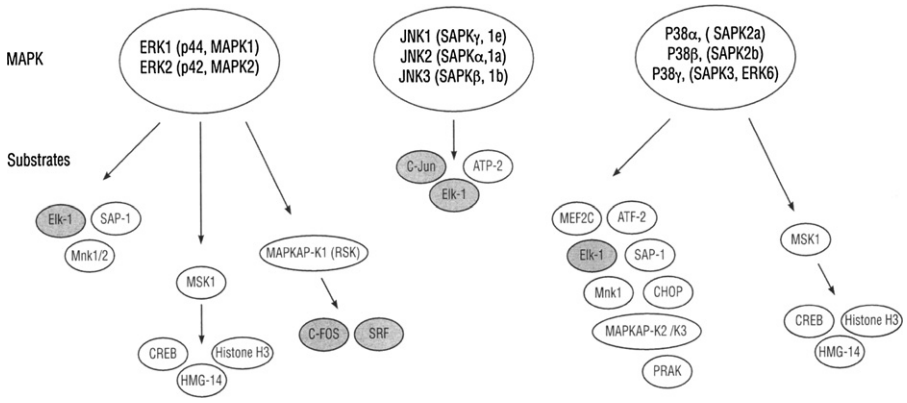

Fig. 2. The four mitogen activated protein kinase (MAPK) signaling cascades identified to date are: extracellular signal regulated kinase 1/2 (ERK), c-Jun-terminal kinase (JNK), p38MAPK and stress activated protein kinase (SAPK). Elements of the three MAPkinase pathways that have been identified as activated by EMF are shown as the shaded circles.

following ischemia. This effect occurred in the absence of measurable increased temperature.

3. EMF interaction with signaling pathways

EMF penetrate cells unattenuated and so can interact directly with the DNA in the cell nucleus, as well as other cell constituents. However, biological agents are impeded by membranes and require special mechanisms to gain access to the cell interior. Friedman et al. [23] have demonstrated that the initial step in transmitting extracellular information from the plasma membrane to the nucleus of the cell occurs when NADH oxidase rapidly generates reactive oxygen species (ROS). These ROS stimulate matrix metalloproteinases that allow them to cleave and release heparin binding epidermal growth factor. This secreted factor activates the epidermal growth receptor, which in turn activates the extracellular signal regulated kinase 1\2 (ERK) cascade. The ERK cascade is one of the four mitogen-activated protein kinase (MAPK) signaling cascades that regulate transcriptional activity in response to extracellular stimuli. The elements of the three MAPK signaling cascades implicated in exposures to ELF and RF are highlighted in Fig. 2.

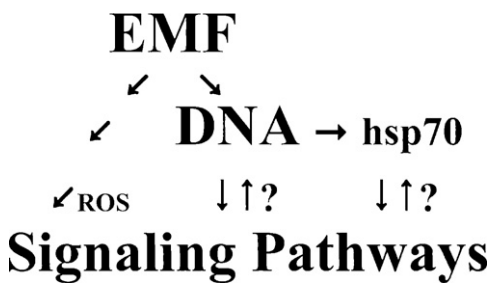

Fig. 3. The signaling pathways and the stress response are activated by EMF. The activation mechanisms discussed in the text are indicated by arrows. In the stress response, DNA activation leads to hsp synthesis and may be due to direct EMF interaction with DNA. The signaling pathways are activated by reactive oxygen species (ROS) that are probably generated by EMF. Possible interactions between the pathways, DNA and hsp are indicated with question marks. In any case, EMF leads to activation of all the processes shown.

The four MAPK cascades are: (1) ERK, (2) c-Jun-terminal kinase (JNK), (3) stress activated protein kinase (SAPK) and (4) p38SAPK. Each of the cascades is composed of three to six tiers of protein kinases, and their signals are transmitted by sequential phosphorylation and activation of the protein kinases in each of the tiers. The result is activation of a large number of regulatory proteins, which include a set of transcription factors, e.g., c-Jun, c-Fos, hsp27 and hsp70. Activation of the stress response is accompanied by activation of specific signal transduction cascades involved in regulating cell proliferation, differentiation and metabolism [24–26]. The MAPK pathways have been characterized in several cell types [24,27–30]. Exposure to non-thermal ELF as well as thermal RF affects the expression of many cellular proteins [23–25] (Fig. 3).

The elevated expression of these protein transcription factors participate in the induction of various cellular processes, including several that are affected by cell phones, e.g., replication and cell-cycle progression [25,31] and apoptosis [32]. RF fields have been shown to activate specific transcription factor binding that stimulate cell proliferation and induce stress proteins [25,33]. It has been reported [31] that within 10 min of cell phone exposures, two MAPKinase cascades, p38 and ERK1\2, are activated. Both ELF and RF activate the upregulation of the HSP70 gene and induction of elevated levels of the hsp70 protein. This effect on RNA transcription and protein stability is controlled by specific protein transcription factors that are elements of the mitogen MAPK cascade.

EMF also stimulate serum response factor which binds to the serum response element (SRE) through ERK MAPK activation and is associated with injury and repair *in vivo* and *in vitro*. The SRE site is on the promoter of an early response gene, c-fos, which under specific cellular circumstances has oncogenic properties. The c-fos promoter is EMF-sensitive; a 20 min exposure to 60 Hz 80mG fields significantly increases c-*fos* gene expression [34]. The SRE accessory protein,

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Elk-1, contains a growth-regulated transcriptional activation domain. ERK phosphorylation potentiates Elk-1 and transactivation at the c-*fos* SRE [29].

During the past twenty years, the growing use of cellular phones has aroused great concern regarding the health effects of exposure of the brain to 900 MHz RF waves. Despite claims that the energy level is too low to induce changes in DNA and that the devices are safe, the non-thermal effects that have been demonstrated at both ELF and RF exposure levels can cause physiological changes in cells and tissues even at the level of DNA. Finally, it should be mentioned that some of the pathways described in this section also have roles in protein synthesis via RNA polymerase III, an enzyme in oncogenic pathways [35] and could, therefore, provide a mechanistic link between cancer and EMF exposure.

4. Cells affected by the stress response

Reviews on EMF and the stress response have appeared for the ELF range [13] and for the RF range [36]. The most recent review was published online in section 7 of the Bioinitiative Report [9], and it summarized both ELF and RF studies, mainly at frequencies 50 Hz, 60 Hz, 900 MHz and 1.8 GHz. The citations in that review were not exhaustive, but the different frequencies and biological systems represent the diversity of results on stimulation of DNA and stress protein synthesis in many different cells. It is clear that the stress response does not occur in reaction to EMF in all types of cells, and sometimes because of the use of tissue cultured cell lines, even the same cell line can give opposite results in the same laboratory [37].

Many different types of cells have been shown to respond to EMF, both *in vivo* and *in vitro*, including epithelial, endothelial and epidermal cells, cardiac muscle cells, fibroblasts, yeast, *E. coli*, developing chick eggs, and dipteran cells (see Bioinitiative Report [9], section 7). Tissue cultured cells are less likely to show an effect of EMF, probably because immortalized cells have been changed significantly to enable them to live indefinitely in unnatural laboratory conditions. This may also be true of cancer cells, although some (e.g., MCF7 breast cancer cells) have responded to EMF [38,39], and in HL60 cells, one cell line responds to EMF while another does not [24]. Czyz et al. [16] found that p53-deficient embryonic stem cells showed an increased EMF response, but the wild type did not.

A broad study of genotoxic effects (i.e., DNA damage) in different kinds of cells [40] found no effects with lymphocytes, monocytes and skeletal muscle cells, but did find effects with fibroblasts, melanocytes and rat granulosa cells. Other studies [41,42] have also found that the blood elements, such as lymphocytes and monocytes are natural cells that have not responded. Since mobile cells can easily move away from a stress, there would be little selective advantage and evolutionary pressure for developing the stress response. The lack of response by skeletal muscle cells is related to the need to desensitize the cells to excessive heating during activity. Unlike slow muscle fibers that do synthesize hsp70, cells containing fast muscle fibers do not synthesize hsp70 to protect them from over-reacting to the high temperatures reached a during activity.

Table 1
Biological thresholds in the ELF range.

Biological system	Threshold (μT)[a]	Reference
Acceleration of reaction rates		
Na,K-ATPase	0.2–0.3	Blank and Soo [49]
cytochrome oxidase	0.5–0.6	Blank and Soo [43]
ornithine decarboxylase	∼2	Mullins et al. [58]
malonic acid oxidation	<0.5	Blank and Soo [59]
Biosynthesis of stress proteins		
HL60, Sciara, yeast,	<0.8	Goodman et al. [11]
breast (HTB124, MCF7)	<0.8	Lin et al. [39]
chick embryo (anoxia)	∼2	DiCarlo et al. [60]
Breast cancer (MCF7) cell growth		
block melatonin inhibition	0.2 < 1.2	Liburdy et al. [38]
Leukemia epidemiology	0.3–4	Ahlbom et al. [61] Greenland et al. [62]

[a] The estimated values are for departures from the baseline, although Mullins et al. (1999) and DiCarlo et al. (2000) generally give inflection points in the dose–response curves. The leukemia epidemiology values are not experimental and are listed for comparison.

5. EMF–DNA interaction mechanisms: electron transfer

The biochemical compounds in living cells are composed of charges and dipoles that can interact with electric and magnetic fields by various mechanisms. An example discussed earlier is the generation of reactive oxygen species (ROS) in activation of the ERK signaling cascade. The cellular stress response leading to the synthesis of stress proteins is also activated by EMF. However, the specific reaction is not known, except that it is stimulated by very weak EMF. For this reason, our focus has been on molecular processes that are most sensitive to EMF and that could cause the DNA to come apart to initiate biosynthesis. We have suggested that direct EMF interaction with electrons in DNA is likely for the following reasons:

- The largest effects of EMF would be expected on electrons because of their high charge to mass ratio. At the sub-atomic level, one assumes that electrons respond instantaneously compared to protons and heavier atomic nuclei, as in the Born-Oppenheimer Approximation. The very low field strengths and durations that activate the stress response and other reactions (Table 1) suggest interaction with electrons, and make ion-based mechanisms unlikely.
- Weak ELF fields have been shown to affect the rates of electron transfer reactions [43,44]. A 10 μT magnetic field exerts a very small force of only $\sim 10^{-20}$ N on a unit charge,

but this force can move an isolated electron more than a bond length, ∼1 nm, in ∼1 nanosecond.

- There is a specific EMF responsive DNA sequence that is associated with the response to EMF (Fig. 1), and that retains this property when transfected
- Displacement of electrons in DNA would cause local charging that has been shown to lead to disaggregation of biopolymers [45].
- As the energy in an EMF stimulus increases, there is an increase in single strand breaks, followed by double strand breaks, suggesting an interaction with EMF at all energy levels [46].

Effects of EMF on electrons in chemical reactions were detected indirectly in studies on the Na,K-ATPase [47], a ubiquitous enzyme that establishes the normal Na and K ion gradients across cell membranes. Electric and magnetic fields, each accelerated the reaction only when the enzyme was relatively inactive. It is reasonable to assume that the threshold response occurs when the same charge is affected by the two fields, so the velocity (v) of the charge (q) could be calculated from these measurements and its nature determined. Assuming both fields exert the same force at the threshold, the electric (E) and the magnetic (B) forces should be equal.

$$F = qE = qvB. \quad (1)$$

From this $v = E/B$, the ratio of the threshold fields, and by substituting the measured thresholds [48,49], $E = 5 \times 10^{-4}$ V/m and $B = 5 \times 10^{-7}$T (0.5 μT), we obtain $v = 10^3 m/s$. This very rapid velocity, similar to that of electrons in DNA [50], indicated that electrons were probably involved in the ion transport mechanism of the Na,K-ATPase [47]. An electron moving at a velocity of 10^3 m/s crosses the enzyme (∼10^{-8} m) before the ELF field has had a chance to change. This means that a low frequency sine wave signal is effectively a repeated DC pulse. This is true of all low frequency effects on fast moving electrons.

Studies of effects of EMF on electron transfer in cytochrome oxidase, ATP hydrolysis by the Na,K-ATPase, and the Belousov–Zhabotinski (BZ) redox reaction, have led to certain generalizations:

- EMF can accelerate reaction rates, including electron transfer rates
- EMF acts as a force that competes with the chemical forces in a reaction. The effect of EMF varies inversely with the intrinsic reaction rate, so EMF effects are only seen when intrinsic rates are low. (This is in keeping with the therapeutic efficacy of EMF on injured tissue, while there is usually little or no effect on normal tissue.)
- Experimentally determined thresholds are low (∼0.5 μT) and comparable to levels found by epidemiology. See Table 1.
- Effects vary with frequency, with different optima for the reactions studied: The two enzymes showed broad frequency optima close to the reaction turnover numbers for Na,K-ATPase (60 Hz) and cytochrome oxidase (800 Hz), suggesting that EMF interacted optimally when in synchrony with the molecular kinetics. This is not true for EMF interactions with DNA, which are stimulated in both ELF and RF ranges and do not appear to involve electron transfer reactions with well-defined kinetics.

Probably the most convincing evidence for a frequency sensitive mechanism that involves stimulation of DNA is activation of protein synthesis in striated muscle. In this natural process, specific muscle proteins are synthesized by varying the rate of the (electrical) action potentials in the attached nerves [51]. The ionic currents of the action potentials that flow along and through the muscle membranes, also pass through the muscle cell nuclei that contain the DNA codes for the muscle proteins. Two frequencies were studied in muscle, high (100 Hz) and low (10 Hz) frequency, corresponding to the frequencies of the fast muscles and slow muscles that have different contraction rates and different muscle proteins. In the experiments, either the fast or slow muscle proteins were synthesized at the high or low frequency stimulation rates corresponding to the frequency of the action potentials. The clear dependence of the protein composition on the frequency of the action potentials indicates a relation between stimulation and activation of DNA in muscle physiology. The process is undoubtedly far more complicated and unlikely to be a simple electron transfer reaction as with cytochrome oxidase. It is more probable that an entire region of DNA coding for a group of related proteins is activated simultaneously.

A mechanism based on electron movement is in keeping with the mV/m electric field and μT magnetic field thresholds that affect the Na,K-ATPase. The very small force on a charge (∼10^{-20} N) can affect an electron, but is unlikely to have a direct effect on much more massive ions and molecules, especially if they are hydrated. Ions are affected by the much larger DC electric fields of physiological membrane processes. The low EMF energy can move electrons, cause small changes in charge distribution and release the large hydration energy tied up in protein and DNA structures [3]. Electrons have been shown to move in DNA at great speed [50], and we have suggested that RF and ELF fields initiate the stress response by directly interacting and accelerating electrons moving within DNA [52,53].

A mechanism based on electron movement also provides insight into why the same stress response is stimulated by both ELF and RF even though the energies of the two stimuli differ by orders of magnitude. A typical ELF cycle at 10^2Hz lasts 10^{-2} s and a typical RF cycle at 10^{11} Hz lasts 10^{-11} s. Because the energy is spread over a different number of cycles/second in the two ranges, the energy/cycle is the same in both ELF and RF ranges. Since electron movement occurs much faster than the change of field, both frequencies are seen by rapidly moving electrons as essentially DC pulses. Each cycle contributes to electron movement at both

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frequencies, but more rapidly at the higher frequency. The fluctuation of protons between water molecules in solution at a frequency of about 10^{12} Hz [54] gives an indication of the speed of electron movement, and may suggest an upper limit of the frequency in which sine wave EMF act as DC pulses.

6. DNA biology and the EM spectrum

Research on DNA and the stress response has shown that the same biology occurs across divisions of the EM spectrum, and that EMF safety standards based on cellular measures of potential harm should be much stricter. These data also raise questions about the utility of spectrum sub-divisions as the basis for properly assessing biological effects and setting separate safety standards for the different sub-divisions. The frequencies of the EM spectrum form a continuum, and division into frequency bands is only a convenience that makes it easier to assign and regulate different portions of the spectrum for practical uses, such as the different design requirements of devices for EMF generation and measurement. Except for the special case of the visual range, the frequency bands are not based on biology, and the separate bands now appear to be a poor way of dealing with biological responses needed for evaluating safety. The DNA studies indicate the need for an EMF safety standard rooted in biology and a rational basis for assessing health implications.

DNA responses to EMF can be used to create a single scale for evaluation of EMF dose because:

- The same biological responses are stimulated in ELF and RF ranges.
- The intensity of EMF interactions with DNA leads to greater effects on DNA as the energy increases with frequency. In the ELF range, the DNA is only activated to initiate protein synthesis, while single and double strand breaks occur in the more energetic RF and ionizing ranges.

A scale based on DNA biology also makes possible an approach to a quantitative relation between EMF dose and disease. This can be done by utilizing the data banks that have been kept for A-bomb exposure and victims of nuclear accidents, data that link exposure to ionizing radiation and subsequent development of cancer. Utilizing experimental studies of DNA breaks with ionizing radiation, it is possible in principle to relate cancer incidence to EMF exposures. It should be possible to determine single and double strand breaks in a standard preparation of DNA, caused by exposure to EMF for a specified duration, under standard conditions. Although many studies of DNA damage and repair rates under different conditions would be needed, this appears to be a possible experimental approach to assessing the relation between EMF exposure and disease.

7. The stress response and safety standards

Most scientists believe that basic research eventually pays off in practical ways. This has certainly been true of EMF research on the stress response, where EMF stimulated stress proteins have been used to minimize damage to ischemic tissues on reperfusion. However, more importantly, biological effects stimulated by both ELF and RF have shown that the standards used for developing safety guidelines are not protective of cells.

First and foremost, it is important to realize that the stress response occurs in reaction to a potentially harmful environmental influence. The stress response is an unambiguous indication that cells react to EMF as potentially harmful. It is therefore an indication of compromised cell safety, given by the cell, in the language of the cell. The low threshold level of the stress response shows that the current safety standards are much too high to be considered safe.

In general, cellular processes are unusually sensitive to fields in the environment. The biological thresholds in the ELF range (Table 1) are in the range of 0.5–1.0 μT—not very much higher than the ELF backgrounds of ~0.1 μT. The relatively low field strengths that can affect biochemical reactions is a further indication that cells are able to sense potential danger long before there is an increase in temperature.

EMF research has also shown that exposure durations do not have to be prolonged to have an effect. Litovitz et al. [55,56], working with the enzyme ornithine decarboxylase, showed an EMF response when cells were exposed for only 10 s to ELF or ELF modulated 915 MHz, providing that the exposure was continuous. Gaps in the sine wave resulted in a reduced response, and interference with the sine wave in the form of superimposed ELF noise also reduced the response [57]. The interfering effect of noise has been shown in the RF range by Lai and Singh [46], who reported that noise interferes with the ability of an RF signal to cause breaks in DNA strands. The decreased effect when noise is added to a signal is yet another indication that EMF energy is not the critical factor in causing a response. In fact, EMF noise appears to offer a technology for mitigating potentially harmful effects of EMF in the environment.

EMF research has shown that the thermal standard used by agencies to measure safety is at best incomplete, and in reality not protective of potentially harmful non-thermal fields. Non-thermal ELF mechanisms are as effective as thermal RF mechanisms in stimulating the stress response and other protective mechanisms. The current safety standard based on thermal response is fundamentally flawed, and not protective.

Finally, since both ELF and RF activate the same biology, simultaneous exposure to both is probably additive and total EMF exposure is important. Safety standards must consider total EMF exposure and not separate standards for ELF and RF ranges.

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Electromagnetic fields and DNA damage

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Abstract

A major concern of the adverse effects of exposure to non-ionizing electromagnetic field (EMF) is cancer induction. Since the majority of cancers are initiated by damage to a cell's genome, studies have been carried out to investigate the effects of electromagnetic fields on DNA and chromosomal structure. Additionally, DNA damage can lead to changes in cellular functions and cell death. Single cell gel electrophoresis, also known as the 'comet assay', has been widely used in EMF research to determine DNA damage, reflected as single-strand breaks, double-strand breaks, and crosslinks. Studies have also been carried out to investigate chromosomal conformational changes and micronucleus formation in cells after exposure to EMF. This review describes the comet assay and its utility to qualitatively and quantitatively assess DNA damage, reviews studies that have investigated DNA strand breaks and other changes in DNA structure, and then discusses important lessons learned from our work in this area.
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Keywords: Electromagnetic field; DNA damage; Comet assay; Radiofrequency radiation; Cellular telephone

1. The comet assay for measurement of DNA strand breaks

DNA is continuously damaged by endogenous and exogenous factors and then repaired by DNA repair enzymes. Any imbalance in damage and repair and mistakes in repair result in accumulation of DNA damage. Eventually, this will lead to cell death, aging, or cancer. There are several types of DNA lesions. The common ones that can be detected easily are DNA strand breaks and DNA crosslinks. Strand breaks in DNA are produced by endogenous factors, such as free radicals generated by mitochondrial respiration and metabolism, and by exogenous agents, including UV, ionizing and non-ionizing radiation, and chemicals.

There are two types of DNA strand breaks: single- and double-strand breaks. DNA single-strand breaks include frank breaks and alkali labile sites, such as base modification, deamination, depurination, and alkylation. These are the most commonly assessed lesions of DNA. DNA double-strand breaks are very critical for cells and usually they are lethal. DNA strand breaks have been correlated with cell death [1–5], aging [6–8] and cancer [9–13].

Several techniques have been developed to analyze single- and double-strand breaks. Most commonly used is microgel electrophoresis, also called the 'comet assay' or 'single cell gel electrophoresis'. This technique involves mixing cells with agarose, making microgels on a microscope slide, lysing cells in the microgels with salts and detergents, removing proteins from DNA by using proteinase K, unwinding/equilibrating and electrophoresing DNA (under highly alkaline condition for assessment of single-strand breaks or under neutral condition for assessment of DNA double-strand breaks), fixing the DNA, visualizing the DNA with a fluorescent dye, and then analyzing migration patterns of DNA from individual cells with an image analysis system.

The comet assay is a very sensitive method of detecting single- and double-strand breaks if specific criteria are met. Critical criteria include the following. Cells from tissue culture or laboratory animals should be handled with care to minimize DNA damage, for instance, by avoiding light and high temperature. When working with animals exposed to EMF *in vivo*, it is better to anesthetize the animals with CO_2 before harvesting tissues for assay. Antioxidants

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such as albumin and sucrose, or spin-trap molecules such as α-phenyl-*tert*-butyl nitrone (PBN), should be added during dispersion of tissues into single cells. Cells should be lysed at 0–4 °C to minimize DNA damage by endonucleases. Additionally, antioxidants such as tris and glutathione, and chelators such as EDTA, should be used in the lysing solution. High concentrations of dimethylsulfoxide (DMSO) should be avoided due to its chromatin condensing effect. Treatment with proteinase K (PK; lyophilized DNAse-free proteinase-K from Amresco is ideal) at a concentration of 0.5–1 mg/ml (depending upon cell type and number of cells in the microgel) should be used for 1–2 h at 37 °C to reveal all possible strand breaks which otherwise may go undetected due to DNA–protein crosslinks. Longer times in PK will lead to loss of smaller pieces of DNA by diffusion. Glass slides should be chosen based on which high resolution agarose (3:1 high resolution agarose from Amresco is ideal) will stick well to the slide and on the ability of the specimen to be visualized without excessive fluorescence background. Choice of an electrophoresis unit is important to minimize slide-to-slide variation in DNA migration pattern. A unit with uniform electric field and buffer recirculation should be used. Electrophoresis buffers should have antioxidants and chelators such as DMSO and EDTA. DNA diffusion should be minimized during the neutralization step by rapidly precipitating the DNA. Staining should employ a sensitive fluorescent dye, such as the intercalating fluorescent labeling dye YOYO-1. A cell-selection criteria for analysis should be set before the experiment, such as not analyzing cells with too much damage, although, the number of such cells should be recorded.

There are different versions of the comet assay that have been modified to meet the needs of specific applications and to improve sensitivity. Using the most basic form of the assay, one should be able to detect DNA strand breaks in human lymphocytes that were induced by 5 rad of gamma-ray [14,15].

2. Radiofrequency radiation (RFR) and DNA damage

In a series of publications, Lai and Singh [16–19] reported increases in single- and double-strand DNA breaks, as measured by the comet assay, in brain cells of rats exposed for 2 h to a 2450-MHz RFR at whole body specific absorption rate (SAR) between 0.6 and 1.2 W/kg. The effects were blocked by antioxidants, which suggested involvement of free radicals. At the same time, Sarkar et al. [20] exposed mice to 2450-MHz microwaves at a power density of 1 mW/cm^2 for 2 h/day over a period of 120, 150, and 200 days. Rearrangement of DNA segments were observed in testis and brain of exposed animals. Their data also suggested breakage of DNA strands after RFR exposure. Phillips et al. [21] were the first to study the effects of two forms of cell cellular phone signals, known as TDMA and iDEN, on DNA damage in Molt-4 human lymphoblastoid cells using the comet assay. These cells were exposed to relatively low intensities of the fields (2.4–26 μW/g) for 2–21 h. They reported both increased and decreased DNA damage, depending on the type of signal studied, as well as the intensity and duration of exposure. They speculated that the fields may affect DNA repair in cells. Subsequently, different groups of researchers have also reported DNA damage in various types of cells after exposure to cell phone frequency fields. Diem et al. [22] exposed human fibroblasts and rat granulosa cells to cell phone signal (1800 MHz; SAR 1.2 or 2 W/kg; different modulations; for 4, 16 and 24 h; intermittent 5 min on/10 min off or continuous). RFR exposure induced DNA single- and double-strand breaks as measured by the comet assay. Effects occurred after 16 h of exposure to different cell phone modulations in both cell types. The intermittent exposure schedule caused a significantly stronger effect than continuous exposure. Gandhi and Anita [23] reported increases in DNA strand breaks and micronucleation in lymphocytes obtained from cell phone users. Markova et al. [24] reported that GSM signals affected chromatin conformation and γ-H2AX foci that co-localized in distinct foci with DNA double-strand breaks in human lymphocytes. The effect was found to be dependent on carrier frequency. Nikolova et al. [25] reported a low and transient increase in DNA double-strand breaks in mouse embryonic stem cells after acute exposure to a 1.7-GHz field. Lixia et al. [26] reported an increase in DNA damage in human lens epithelial cells at 0 and 30 min after 2 h of exposure to a 1.8-GHz field at 3 W/kg. Sun et al. [27] reported an increase in DNA single-strand breaks in human lens epithelial cells after 2 h of exposure to a 1.8-GHz field at SARs of 3 and 4 W/kg. DNA damage caused by the field at 4 W/kg was irreversible. Zhang et al. [28] reported that an 1800-MHz field at 3.0 W/kg induced DNA damage in Chinese hamster lung cells after 24 h of exposure. Aitken et al. [29] exposed mice to a 900-MHz RFR at a SAR of 0.09 W/kg for 7 days at 12 h per day. DNA damage in caudal epididymal spermatozoa was assessed by quantitative PCR (QPCR) as well as by alkaline and pulsed-field gel electrophoresis. Gel electrophoresis revealed no significant change in single- or double-strand breaks in spermatozoa. However, QPCR revealed statistically significant damage to both the mitochondrial genome and the nuclear β-globin locus. Changes in sperm cell genome after exposure to 2450-MHz microwaves have also been reported previously by Sarkar et al. [20]. Related to this are several publications that have reported decreased motility and changes in morphology in isolated sperm cells exposed to cell phone radiation [30], sperm cells from animals exposed to cell phone radiation [31], and cell phone users [32–34]. Some of these *in vivo* effects could be caused by hormonal changes [35,36].

There also are studies reporting no significant effect of cell phone RFR exposure on DNA damage. After RFR-induced DNA damage was reported by Lai and Singh [16] using 2450-MHz microwaves and after the report of Phillips et al. [21] on cell phone radiation was published, Motorola funded a series of studies by Roti Roti and colleagues [37] at

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Washington University to investigate DNA strand breaks in cells and animals exposed to RFR. None of the studies reported by this group found significant effects of RFR exposure on DNA damage [38–40]. However, a different version of the comet assay was used in these studies. More recently, four additional studies from the Roti-Roti laboratories also reported no significant effects on DNA damage in cells exposed to RFR. Li et al. [41] reported no significant change in DNA strand breaks in murine C3H10T1/2 fibroblasts after 2 h of exposure to 847.74- and 835.02-MHz fields at 3–5 W/kg. Hook et al. [42] showed that a 24-h exposure of Molt-4 cells to CDMA, FDMA, iDEN or TDMA-modulated RFR did not significantly alter the level of DNA damage. Lagroye et al. [43,44] also reported no significant change in DNA strand breaks, protein–DNA crosslinks, and DNA–DNA crosslinks in cells exposed to 2450-MHz RFR.

From other laboratories, Vijayalaxmi et al. [45] reported no increase in DNA stand breaks in human lymphocytes exposed *in vitro* to 2450-MHz RFR at 2.135 W/kg for 2 h. Tice et al. [46] measured DNA single-strand breaks in human leukocytes using the comet assay after exposure to various forms of cell phone signals. Cells were exposed for 3 or 24 h at average SARs of 1.0–10.0 W/kg. Exposure for either 3 or 24 h did not induce a significant increase in DNA damage in leukocytes. McNamee et al. [47–49] found no significant increase in DNA breaks and micronucleus formation in human leukocytes exposed for 2 h to a 1.9-GHz field at SAR up to 10 W/kg. Zeni et al. [50] reported that a 2-h exposure to 900-MHz GSM signal at 0.3 and 1 W/kg did not significantly affect levels of DNA strand breaks in human leukocytes. Sakuma et al. [51] exposed human glioblastoma A172 cells and normal human IMR-90 fibroblasts from fetal lungs to cell phone radiation for 2 and 24 h. No significant changes in DNA strand breaks were observed up to a SAR of 800 mW/kg. Stronati et al. [52] showed that 24 h of exposure to 935-MHz GSM basic signal at 1 or 2 W/Kg did not cause DNA strand breaks in human blood cells. Verschaeve et al. [53] reported that long-term exposure (2 h/day, 5 days/week for 2 years) of rats to 900-MHz GSM signal at 0.3 and 0.9 W/kg did not significantly affect levels of DNA strand breaks in cells.

3. Extremely low frequency electromagnetic fields (ELF EMF) and DNA damage

To complete the picture, a few words on the effects of ELF EMF are required, since cell phones also emit these fields and they are another common form of non-ionizing EMF in our environment. Quite a number of studies have indicated that exposure to ELF EMF could lead to DNA damage [54–69]. In addition, two studies [70,71] have reported effects of ELF fields on DNA repair mechanisms. Free radicals and interaction with transitional metals (e.g., iron) [60,62,63,69] have also been implicated to play a role in the genotoxic effects observed after exposure to these fields.

4. Some considerations on the effects of EMF on DNA

From this brief literature survey, no consistent pattern of RFR exposure inducing changes in or damage to DNA in cells and organisms emerges. However, one can conclude that under certain conditions of exposure, RFR is genotoxic. Data available are mainly applicable only to radiation exposure that would be typical during cell phone use. Other than the study of Phillips et al. [21], there is no indication that RFR at levels that one can experience in the vicinity of base stations and RF-transmission towers could cause DNA damage.

Differences in experimental outcomes are expected since many factors could influence the outcome of experiments in EMF research. Any effect of EMF has to depend on the energy absorbed by a biological organism and on how the energy is delivered in space and time. Frequency, intensity, exposure duration, and the number of exposure episodes can affect the response, and these factors can interact with each other to produce different effects. In addition, in order to understand the biological consequence of EMF exposure, one must know whether the effect is cumulative, whether compensatory responses result, and when homeostasis will break down. The contributions of these factors have been discussed in a talk given by one us (HL) in Vienna, Austria in 1998 [72].

Radiation from cell phone transmission has very complex patterns, and signals vary with the type of transmission. Moreover, the technology is constantly changing. Research results from one types of transmission pattern may not be applicable to other types. Thus, differences in outcomes of the research on genotoxic effects of RFR could be explained by the many different exposure conditions used in the studies. An example is the study of Phillips et al. [21], which demonstrated that different cell phone signals could cause different effects on DNA (i.e., an increase in strand breaks after exposure to one type of signal and a decrease with another). This is further complicated by the fact that some of the studies listed above used poor exposure procedures with very limited documentation of exposure parameters, e.g., using an actual cell phone to expose cells and animals, thus rendering the data from these experiments as questionable.

Another source of influence on experimental outcome is the cell or organism studied. Many different biological systems were used in the genotoxicity studies. Different cell types [73] and organisms [74,75] may not all respond similarly to EMF.

Comment about the comet assay also is required, since it was used in many of the EMF studies to determine DNA damage. Different versions of the assay have been developed. These versions have different detection sensitivities and can be used to measure different aspects of DNA strand breaks. A comparison of data from experiments using different versions of the assay could be misleading. Another concern is that most of the comet assay studies were carried out by experimenters who had no prior experience with this technique and mistakes

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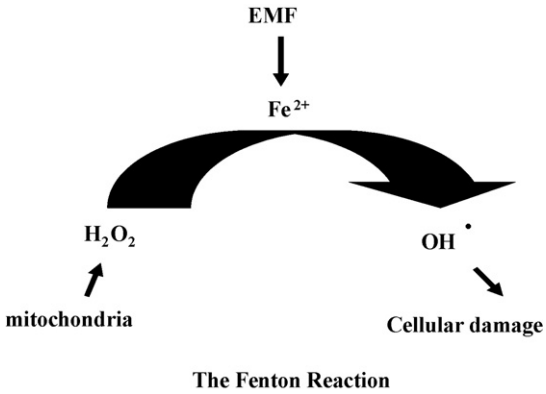

Fig. 1. A representation of the Fenton reaction and its role as a mediator in EMF-induced bioeffects.

were made. For example, in the study by Lagroye et al. [43] to investigate the effect of PK digestion on DNA migration after RFR exposure, PK was added to a lysing solution containing the detergent Triton X-100, which would inactivate the enzyme. Our experience indicates that the comet assay is a very sensitive and requires great care to perform. Thus, different detection sensitivities could result in different laboratories, even if the same procedures are followed. One way to solve this problem of experimental variation is for each research team to report the sensitivity of their comet assay, e.g., the threshold of detecting strand breaks in human lymphocytes exposed to X-rays. This information has generally not been provided for EMF-genotoxicity studies. Interestingly, when such information was provided, a large range of sensitivities have been reported. Malyapa et al. [40] reported a detection level of 0.6 cGy of gamma radiation in human lymphocytes, whereas McNamee et al. [76] reported 10–50 cGy of X-irradiation in lymphocytes, which is much higher than the generally acceptable detection level of the comet assay [15].

A drawback in the interpretation and understanding of experimental data from bioelectromagnetics research is that there is no general acceptable mechanism on how EMF affects biological systems. The mechanism by which EMF produces changes in DNA is unknown. Since the energy level associated with EMF exposure is not sufficient to cause direct breakage of chemical bonds within molecules, the effects are probably indirect and secondary to other induced biochemical changes in cells.

One possibility is that DNA is damaged by free radicals that are formed inside cells. Free radicals affect cells by damaging macromolecules, such as DNA, protein, and membrane lipids. Several reports have indicated that EMF enhances free radical activity in cells [18,19,61,62,77,78], particularly via the Fenton reaction [62]. The Fenton reaction is a process catalyzed by iron in which hydrogen peroxide, a product of oxidative respiration in the mitochondria, is converted into hydroxyl free radicals, which are very potent and cytotoxic molecules (Fig. 1).

It is interesting that ELF EMF has also been shown to cause DNA damage. Furthermore, free radicals have been implicated in this effect of ELF EMF. This further supports the view that EMF affects DNA via an indirect secondary process, since the energy content of ELF EMF is much lower than that of RFR. Effects via the Fenton reaction predict how a cell would respond to EMF. For instance:

(1) Cells that are metabolically active would be more susceptible to EMF, because more hydrogen peroxide is generated by mitochondria to fuel the reaction.
(2) Cells that have high level of intracellular free iron would be more vulnerable to EMF. Cancer cells and cells undergoing abnormal proliferation have higher concentrations of free iron because they uptake more iron and have less efficient iron storage regulation. Thus, these cells could be selectively damaged by EMF. Consequently, this suggests that EMF could potentially be used for the treatment of cancer and hyperplastic diseases. The effect could be further enhanced if one could shift anaerobic glycolysis of cancer cells to oxidative glycolysis. There is quite a large database of information on the effects of EMF (mostly in the ELF range) on cancer cells and tumors. The data tend to indicate that EMF could retard tumor growth and kill cancer cells. One consequence of this consideration is that epidemiological studies of cancer incidence in cell phone users may not show a risk at all or even a protection effect.
(3) Since the brain is exposed to rather high levels of EMF during cell phone use, the consequences of EMF-induced genetic damage in brain cells are of particular importance. Brain cells have high levels of iron. Special molecular pumps are present on nerve cell nuclear membranes to pump iron into the nucleus. Iron atoms have been found to intercalate within DNA molecules. In addition, nerve cells have a low capacity for DNA repair, and DNA breaks could easily accumulate. Another concern is the presence of superparamagnetic iron-particles (magnetites) in body tissues, particularly in the brain. These particles could enhance free radical activity in cells and thus increase the cellular-damaging effects of EMF. These factors make nerve cells more vulnerable to EMF. Thus, the effect of EMF on DNA could conceivably be more significant on nerve cells than on other cell types of the body. Since nerve cells do not divide and are not likely to become cancerous, the more likely consequences of DNA damage in nerve cells include changes in cellular functions and in cell death, which could either lead to or accelerate the development of neurodegenerative diseases. Double-strand breaks, if not properly repaired, are known to lead to cell death. Cumulative DNA damage in nerve cells of the brain has been associated with neurodegenerative diseases, such as Alzheimer's, Huntington's, and Parkinson's diseases. However, another type of brain cell, the glial cell, can become cancerous as a result of DNA damage. The question is whether the damaged cells

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would develop into tumors before they are killed by EMF due to over accumulation of genetic damages. The outcome depends on the interplay of these different physical and biological factors—an increase, decrease, or no significant change in cancer risk could result from EMF exposure.

(4) On the other hand, cells with high amounts of antioxidants and antioxidative enzymes would be less susceptible to EMF. Furthermore, the effect of free radicals could depend on the nutritional status of an individual, e.g., availability of dietary antioxidants, consumption of alcohol, and amount of food consumption. Various life conditions, such as psychological stress and strenuous physical exercise, have been shown to increase oxidative stress and enhance the effect of free radicals in the body. Thus, one can also speculate that some individuals may be more susceptible to the effects of EMF exposure.

Additionally, the work of Blank and Soo [79] and Blank and Goodman [80] support the possibility that EMF exposure at low levels has a direct effect on electron transfer processes. Although the authors do not discuss their work in the context of EMF-induced DNA damage, the possibility exists that EMF exposure could produce oxidative damage to DNA.

5. Lessons learned

Whether or not EMF causes biological effects, let alone effects that are detrimental to human health and development, is a contentious issue. The literature in this area abounds with apparently contradictory studies, and as presented in this review, the literature specific to the effects of RFR exposure on DNA damage and repair in various biological systems is no exception. As a consequence of this controversy, there are several key issues that must be addressed—contrary data, weight of evidence, and data interpretation consistent with known science.

Consider that EMF does not share the familiar and comforting physical properties of chemical agents. EMF cannot be seen, tasted, smelled, or felt (except at high intensities). It is relevant, therefore, to ask, in what ways do scientists respond to data, especially if that data are contrary to their scientific beliefs or inconsistent with long-held hypotheses? Often such data are ignored, simply because it contradict what is accepted as conventional wisdom. Careful evaluation and interpretation of data may be difficult, because technologies used to expose biological systems to EMF and methodologies used to assess dosimetry generally are outside the experience of most biomedical scientists. Additionally, it is often difficult to assess differences in methodologies between studies, one or more of which were intended to replicate an original investigation. For instance, Malyapa et al. [40] reported what they claimed to be a replication of the work of Lai and Singh [16]. There were, however, significant differences in the comet analyses used by each group. Lai and Singh precipitated DNA in agarose so that low levels of DNA damage could be detected. Malyapa et al. did not. Lai and Singh treated their samples with PK to digest proteins bound to DNA, thus allowing DNA to move toward the positive pole during electrophoresis (unlike DNA, most proteins are negatively charged, and if they are not removed they will drag the DNA toward the negative pole). The Malyapa et al. study did not use PK. There were other methodological differences as well. Such is also the case in the study of Hook et al. [42], which attempted to replicate the work of Phillips et al. [21]. The latter group used a PK treatment in their comet assay, while the former group did not.

While credibility is enhanced when one can relate data to personal knowledge and scientific beliefs, it has not yet been determined how RFR couples with biological systems or by what mechanisms effects are produced. Even carefully designed and well executed RFR exposure studies may be summarily dismissed as methodologically unsound, or the data may be interpreted as invalid because of inconsistencies with what one believes to be correct. The quintessential example is the belief that exposure to RFR can produce no effects that are not related to the ability of RFR to produce heat, that is, to raise the temperature of biological systems [81,82]. Nonetheless, there are many examples of biological effects resulting from low-level (athermal) RFR exposure [83,84]. Consider here the work of Mashevich et al. [85]. This group exposed human peripheral blood lymphocytes to an 830-MHz signal for 72 h and at different average SARs (SAR, 1.6–8.8 W/kg). Temperatures ranged from 34.5 to 38.5 °C. This group observed an increase in chromosome 17 aneuploidy that varied linearly with SAR. Temperature elevation alone in the range of 34.5–38.5 °C did not produce this genotoxic effect, although significant aneuploidy was observed at higher temperatures of 40–41 °C. The authors conclude that the genotoxic effect of the radiofrequency signal used is elicited through a non-thermal pathway.

Also consider one aspect of the work of Phillips et al. [21]. In that study, DNA damage was found to vary in direction; that is, under some conditions of signal characteristics, signal intensity, and time of exposure, DNA damage increased as compared with concurrent unexposed controls, while under other conditions DNA damage decreased as compared with controls. The dual nature of Phillips et al.'s [21] results will be discussed later. For now consider the relationship of these results to other investigations. Adey et al. [86] performed an *in vivo* study to determine if rats treated *in utero* with the carcinogen ethylnitrosourea (ENU) and exposed to an 836.55-MHz field with North American Digital Cellular modulation (referred to as a TDMA field) would develop increased numbers of central system tumors. This group reported that rather than seeing an increase in tumor incidence in RFR-exposed rats, there was instead a decrease in tumor incidence. Moreover, rats that received no ENU but which were exposed to the TDMA signal also showed a decrease in the number of spontaneous tumors as compared

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with animals exposed to neither ENU nor the TDMA signal. This group postulated that their results may be mechanistically similar to the work of another group. Stammberger et al. [87] had previously reported that rats treated *in utero* with ENU and then exposed to low doses of X-irradiation exhibited significantly reduced incidences of brain tumors in adult life. Stammberger and colleagues [87] hypothesized that low-level X-irradiation produced DNA damage that then induced the repair enzyme 0^6-alkylguanine-DNA alkyltransferase (AT). Numerous groups have since reported that X-irradiation does indeed induce AT activity (e.g., [88,89]). In this context, it is significant that Phillips et al. [21] found that cells exposed *in vitro* to a TDMA signal identical to that used in the study of Adey et al. [86] produced a decrease in DNA damage under specific conditions of intensity and time of exposure (lower intensity, longer time; higher intensity, shorter time). These results raise the intriguing possibility that the decrease in tumor incidence in the study of Adey et al. [86] and the decrease in DNA damage in the study of Phillips et al. [21] both may have been the result of induction of AT activity resulting from DNA damage produced by exposure to the TDMA signal. This remains to be investigated.

Because the issue of RFR-induced bioeffects is contentious, and because the issue is tried in courtrooms and various public forums, a term heard frequently is weight of evidence. This term generally is used to describe a method by which all scientific evidence related to a causal hypothesis is considered and evaluated. This process is used extensively in matters of regulation, policy, and the law, and it provides a means of weighing results across different modalities of evidence. When considering the effects of RFR exposure on DNA damage and repair, modalities of evidence include studies of cells and tissues from laboratory animals exposed *in vivo* to RFR, studies of cells from humans exposed to RFR *in vivo*, and studies of cells exposed *in vitro* to RFR. While weight of evidence is gaining favor with regulators [90], its application by scientists to decide matters of science is often of questionable value. One of the reasons for this is that there generally is no discussion or characterization of what weight of evidence actually means in the context in which it is used. Additionally, the distinction between weight of evidence and strength of evidence often is lacking or not defined, and differences in methodologies between investigators are not considered. Consequently, weight of evidence generally amounts to what Krimsky [90] refers to as a "seat-of-the-pants qualitative assessment." Krimsky points out that according to this view, weight of evidence is "a vague term that scientists use when they apply implicit, qualitative, and/or subjective criteria to evaluate a body of evidence." Such is the case in the reviews by Juutilainen and Lang [91] and Verschaeve and Maes [92]. There is little emphasis on a critical analysis of similarities and differences in biological systems used, exposure regimens, data produced, and investigator's interpretations and conclusions. Rather, there is greater emphasis on the number of publications either finding or not finding an effect of RFR exposure on some endpoint. To some investigators, weight of evidence does indeed refer to the balance (or imbalance) between the number of studies producing apparently opposing results, without regard to critical experimental variables. While understanding the role these variables play in determining experimental outcome could provide remarkable insights into defining mechanisms by which RFR produced biological effects, few seem interested in or willing to delve deeply into the science.

A final lesson can be derived from a statement made by Gos et al. [93] referring to the work of Phillips et al. [21]. Gos and colleagues state, "The results in the latter study (Phillips et al., 1998) are puzzling and difficult to interpret, as no consistent increase or decrease in signal in the comet assay at various SARs or times of exposure was identified." This statement is pointed out because studies of the biological effects of exposure to electromagnetic fields at any frequency are often viewed as outside of or distinct from what many refer to as *mainstream science*. However, what has been perceived as an inconsistent effect is indeed consistent with the observations of bimodal effects reported in hundreds of peer-reviewed publications. These bimodal effects may be dependent on concentration of an agent, time of incubation with an agent, or some other parameter relating to the state of the system under investigation. For instance, treatment of B cells for a short time (30 min) with the protein kinase C activator phorbol 12,13-dibutyrate increased proliferative responses to anti-immunoglobulin antibody, whereas treatment for a longer period of time ($\geq$3 h) suppressed proliferation [94]. In a study of κ-opioid agonists on locomotor activity in mice, Kuzmin et al. [95] reported that higher, analgesic doses of κ-agonists reduced rearing, motility, and locomotion in non-habituated mice. In contrast, lower, subanalgesic doses increased motor activity in a time-dependent manner. Dierov et al. [96] observed a bimodal effect of all-trans-retinoic acid (RA) on cell cycle progression in lymphoid cells that was temporally related to the length of exposure to RA. A final example is found in the work of Rosenstein et al. [97]. This group found that the activity of melatonin on depolarization-induced calcium influx by hypothalamic synaptosomes from rats sacrificed late evening (2000 h) depended on melatonin preincubation time. A short preincubation time (10 min) stimulated uptake, while a longer preincubation (30 min) inhibited calcium uptake. These effects were also dependent on the time of day when the rats were sacrificed. Effects were maximal at 2000 h, minimal at 2400 h, and intermediate at 400 h. At 1000 h, only inhibitory effects of melatonin on calcium uptake were observed. These examples point out that what appears to be inconsistency may instead be real events related to and determined by the agents involved and the state of the biological system under investigation. The results of Phillips et al. [21] may be the result of signal modulation, signal intensity, time of exposure, or state of the cells. The results may indicate a bimodal effect, or they may, as the investigators suggest, represent time- and signal-dependant changes in the balance between damage and repair because of direct or indirect effects of RFR exposure on repair mechanisms.

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6. Summary

Exposure of laboratory animals *in vivo* and of cultured cells *in vitro* to various radiofrequency signals has produced changes in DNA damage in some investigations and not in others. That many of the studies on both sides of this issue have been done well is encouraging from a scientific perspective. RFR exposure does indeed appear to affect DNA damage and repair, and the total body of available data contains clues as to conditions producing effects and methodologies to detect them. This view is in contrast to that of those who believe that studies unable to replicate the work of others are more credible than the original studies, that studies showing no effects cancel studies showing an effect, or that studies showing effects are not credible simply because we do not understand how those effects might occur. Some may be tempted to apply incorrectly the teachings of Sir Karl Popper, one of the great science philosophers of the 20th century. Popper proposed that many examples may lend support to an hypothesis, while only one negative instance is required to refute it [98]. While this holds most strongly for logical subjects, such as mathematics, it does not hold well for more complex biological phenomena that are influenced by stochastic factors. Each study to investigate RFR-induced DNA damage must be evaluated on its own merits, and then studies that both show effects and do not show effects must be carefully evaluated to define the relationship of experimental variables to experimental outcomes and to assess the value of experimental methodologies to detect and measure these outcomes (see Section 2).

The lack of a causal or proven mechanism(s) to explain RFR-induced effects on DNA damage and repair does not decrease the credibility of studies in the scientific literature that report effects of RFR exposure, because there are several plausible mechanisms of action that can account for the observed effects. The relationship between cigarette smoking and lung cancer was accepted long before a mechanism was established. This, however, occurred on the strength of epidemiologic data [99]. Fortunately, relevant epidemiologic data relating long-term cell phone use (>10 years) to central nervous system tumors are beginning to appear [84,100–102], and these data point to an increased risk of acoustic neuroma, glioma and parotid gland tumors.

One plausible mechanism for RFR-induced DNA damage is free radical damage. After finding that two free radical scavengers (melatonin and N-tert-butyl-α-phenylnitrone) prevent RFR-induced DNA damage in rat brain cells, Lai and Singh [62] hypothesized that this damage resulted from free radical generation. Subsequently, other reports appeared that also suggested free radical formation as a result of RFR exposure [103–105]. Additionally, some investigators have reported that non-thermal exposure to RFR alters protein structure and function [106–109]. Scientists are familiar with molecules interacting with proteins through lock-and-key or induced-fit mechanisms. It is accepted that such interactions provide energy to change protein conformation and protein function. Indeed, discussions of these principles are presented in introductory biology and biochemistry courses. Perhaps then it is possible that RFR exposure, in a manner similar to that of chemical agents, provides sufficient energy to alter the structure of proteins involved in DNA repair mechanisms to the extent that their function also is changed. This has not yet been investigated.

When scientists maintain their beliefs in the face of contrary data, two diametrically opposed situations may result. On the one hand, data are seen as either right or wrong and there is no discussion to resolve disparities. On the other hand, and as Francis Crick [110] has pointed out, scientists who hold theoretically opposed positions may engage in fruitful debate to enhance understanding of underlying principles and advance science in general. While the latter certainly is preferable, there are external factors involving economics and politics that keep this from happening. It is time to acknowledge this and embark on the path of fruitful discussion. Great scientific discoveries await.

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Genotoxic effects of radiofrequency electromagnetic fields

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Abstract

101 publications are exploited which have studied genotoxicity of radiofrequency electromagnetic fields (RF-EMF) *in vivo* and *in vitro*. Of these 49 report a genotoxic effect and 42 do not. In addition, 8 studies failed to detect an influence on the genetic material, but showed that RF-EMF enhanced the genotoxic action of other chemical or physical agents. The controversial results may in part be explained by the different cellular systems. Moreover, inconsistencies may depend from the variety of analytical methods being used, which differ considerably with respect to sensitivity and specificity. Taking altogether there is ample evidence that RF-EMF can alter the genetic material of exposed cells i*n vivo* and *in vitro* and in more than one way. This genotoxic action may be mediated by microthermal effects in cellular structures, formation of free radicals, or an interaction with DNA-repair mechanisms.
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Keywords: Gene mutations; Cytogenetic effects; DNA fragmentation; Mechanisms of genotoxicity

1. Introduction

Alterations of genetic information in somatic cells are the key event in the process of carcinogenesis [1,2]. Consequently any agent, which has a genotoxic attribute is suspected also to be cancerogenic. This is the driving force behind the multitude of studies on genotoxicity of radiofrequency electromagnetic fields (RF-EMF), conducted so far. A total of 101 publications on genotoxicity studies of RF-EMF are exploited here, of which 49 report genotoxic effects, subsequently marked as GT(+) (Table 1), 43 do not (Table 2), and 9 find, that RF-EMF do not induce genotoxic events by itself but enhance the genotoxic action of other physical or chemical agents (Table 3). Thus, in contrast to several reviews in the past [3–6], it now became evident that non-thermal genotoxic effects of RF-EMF is convincingly demonstrated by a substantial number of published studies. The studies have been performed with a variety of different test systems – some studies used more than one test system – which will be assigned here to the three principle endpoints of a genotoxic action: (1) effect on chromosomes, (2) DNA fragmentation, and (3) gene mutations.

2. Effect on chromosomes

This group comprises the analysis of numerical or structural anomalies of metaphase chromosomes (CA), sister-chromatid-exchanges (SCEs), and formation of micronuclei (MN). Of the 21 studies using CA, 9 are CA-positive, 11 CA-negative, and 1 reports an RF-induced enhancement of genotoxicity by X-rays. In general proliferating cells are required for the study of chromosomal effects, however, micronuclei have also been analysed in polychromatic erythrocytes and in exfoliated cells, for instance from buccal smears [7,8]. Moreover, aneuploidy rates of distinct chromosomes as well as chromosomal translocations can also be studied in interphase nuclei using fluorescence in situ hybridization (FISH). While structural aberrations detected by conventional CA are mainly lethal to the cell, translocations are persistent and may be passed to the cellular progeny. Using FISH increased levels of aneuploidy of chromosome 1, 10, 11, and 17 have been reported in human blood lymphocytes after RF-EMF exposure [9]. In metaphase chromosomes FISH may increase the sensitivity of chromosomal analysis [10] but this has only once been used for RF-EMF studies [11].

CA brings about to detect a variety of chromosomal aberrations. In contrast, micronuclei originate only from acentric

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Table 1
Publications which report RF-EMF related genotoxic effects.

Reference	Biological system	Genotoxic endpoint	Results and comments
Aitken et al. [45]	Mouse sperm	QPCR and comet assay	Gel electrophoresis revealed no gross evidence of increased single- or double-DNA strand breakage in spermatozoa. However, a detailed analysis of DNA integrity using QPCR revealed damage to both the mitochondrial genome ($p < 0.05$) and the nuclear-globin locus ($p < 0.01$).
Balode [46]	Cow erythrocytes	Micronuclei (MN)	The counting of micronuclei in peripheral erythrocytes gave low average incidences, 0.6 per 1000 in the exposed group and 0.1 per 1000 in the control, but statistically significant ($p < 0.01$) differences were found in the frequency distribution between the control and exposed groups.
Belyaev et al. [47]	Human blood lymphocytes	Chromatin condensation and 53BP1 foci	Decrease in background levels of 53BP1 foci and may indicate decrease in accessibility of 53BP1 to antibodies because of stress-induced chromatin condensation.
Busljeta et al. [48]	Rat hematopoietic tissues	MN	Erythrocyte count, haemoglobin and haematocrit were increased in peripheral blood (days 8 and 15). Concurrently, anuclear cells and erythropoietic precursor cells were decreased ($p < 0.05$) in the bone marrow on day 15, but micronucleated cells' (MNCs) frequency was increased.
d'Ambrosio et al. [49]	Human blood lymphocytes	MN	The micronucleus frequency was not affected by CW exposure; however, a statistically significant micronucleus effect was found following exposure to phase modulated field.
Diem et al. [23]	Human cultured fibroblasts and rat granulosa cells	Alkaline and neutral comet assay	The intermittent exposure showed a stronger effect in the comet assay than continuous exposure.
Ferreira et al. [50]	Rat hematopoietic tissues exposed during embryogenesis	MN	The irradiated group showed a significant increase in MN occurrence.
Fucic et al. [15]	Human blood lymphocytes	MN	X-rays and microwaves were preferentially clastogens while vinyl chloride monomer showed aneugenic activity as well. Microwaves possess some mutagenic characteristics typical of chemical mutagens.
Gadhia et al. [51]	Human blood lymphocytes	Chromosomal aberrations and SCE	There was a significant increase ($p < 0.05$) in dicentric chromosomes among mobile users who were smoker–alcoholic as compared to nonsmoker–nonalcoholic. Synergistic action with MMC, SCEs showed a significant increase among mobile users.
Gandhi and Singh [7]	Human blood lymphocytes and buccal mucosa cells	Chromosomal aberrations and MN	Increased number of micronucleated buccal cells and cytological abnormalities in cultured lymphocytes.
Gandhi, 2005 [52]	Human blood lymphocytes	Comet assay, *in vivo* capillary MN	Mean comet tail length (26.76 ± 0.054 mm; 39.75% of cells damaged) in mobile phone users was highly significant from that in the control group. The *in vivo* capillary blood MNT also revealed highly significant (0.25) frequency of micronucleated cells.
Garaj-Vrhovac et al [53]	Human blood lymphocytes	Chromosomal aberrations and MN	In all experimental conditions, the frequency of all types of chromosomal aberrations was significantly higher than in the control samples. In the irradiated samples the presence of dicentric and ring chromosomes was established. The incidence of micronuclei was also higher in the exposed samples.
Garaj-Vrhovac et al. [54]	Chinese hamster cells V79	DNA synthesis by [3H]thymidine uptake, and chromosomal aberrations	In comparison with the control samples there was a higher frequency of specific chromosome lesions in cells that had been irradiated.
Garaj-Vrhovac et al. [55]	Chinese hamster cells V79	Chromosomal aberrations and MN	Significantly higher frequency of specific chromosome aberrations such as dicentric and ring chromosomes in irradiated cells. The presence of micronuclei in irradiated cells confirmed the changes that had occurred in chromosome structure.
Garaj-Vrhovac et al. [56]	Human blood lymphocytes	MN	Increase in frequency of micronuclei as well as disturbances in the distribution of cells over the first, second and third mitotic division in exposed subjects compared to controls.
Haider et al. [57]	*Tradescantia* flower buds	MN	The results at all exposure sites except one were statistically significant.
Koyama et al. [12]	CHO-K1 cells	MN + kinetochore determination	RF at SAR of 78 W/kg and higher form MN with a particular increase of kinetochore-positive MN and potentiate MN formation induced by bleomycine treatment.
Lai et al. [58]	Rat brain cells	Comet assay	RFR exposure significantly increased DNA double strand breaks in brain cells of the rat, and the effect was partially blocked by treatment with naltrexone.
Lai and Singh [59]	Rat brain cells	Alkaline comet assay	No effects immediately after 2 h of exposure to pulsed microwaves, whereas a dose rate-dependent increase in DNA single strand breaks was found in brain cells of rats at 4 h post-exposure with CW and pulsed waves.

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Lai and Singh [60]	Rat brain cells	Comet assay	Significantly higher levels of DNA single and double strand breaks. Exposure to 'noise' alone did not significantly affect the levels, however, simultaneous 'noise' exposure blocked microwave-induced increases in DNA strand breaks.
Lai and Singh [61]	Rat brain cells	Comet assay	An increase in DNA strand breaks was observed after exposure to either the pulsed or continuous-wave radiation, no significant difference was observed between the effects of the two forms of radiation.
Lai and Singh [35]	Rat brain cells	Comet assay	Treatment immediately before and after RFR exposure with either melatonin or *N*-tert-butyl-alpha-phenylnitrone (PBN) blocks induction of DSB by RFR. It is hypothesized that free radicals are involved in RFR-induced DNA damage in the brain cells of rats.
Lixia et al. [62]	Human lens epithelial cells	Comet assay and BudR incorporation	No DNA breaks at 1 and 2 W/kg but increase 0 and 30 min after exposure to 3 W/kg. Exposure at 2 and 3 W/kg for 2 h significantly increased HsP 70 protein but not mRNA expression.
Maes et al. [63]	Human blood lymphocytes	Chromosome aberrations	Some cytogenetic damage was obtained *in vitro* when blood samples were very close to the antenna. The questionable *in vivo* results (six maintenance workers) are not considered here.
Maes et al. [64]	Human blood lymphocytes	Chromosomal aberrations, SCE, and MN	Marked increase in the frequency of chromosome aberrations (including dicentric chromosomes and acentric fragments) and 19 micronuclei. On the other hand, the microwave exposure did not influence the cell kinetics nor the sister-chromatid-exchange (SCE) frequency.
Markova et al. [65]	Human blood lymphocytes	p53 binding protein and γH2AX foci	MWs from GSM mobile telephones affect chromatin conformation and 53BP1/gamma-H2AX foci similar to heat shock.
Mashevich et al. [66]	Human blood lymphocytes	Chromosomal aberrations	A linear increase in chromosome 17 aneuploidy was observed as a function of the SAR value.
Mazor et al. [9]	Human blood lymphocytes	Aneuploidy rate of Chr. # 1, 10, 11, 17 determined by interphase FISH	Increased levels of aneuploidy in chromosomes 1 and 10 at higher SAR, while for chromosomes 11 and 17 the increases were observed only for the lower SAR.
Nikolova et al. [67]	Mouse nestin-positive neural progenitor cells	Transcript of specific genes and proteins, proliferation, apoptosis, DNA DSB	Down-regulation of neural-specific Nurr1and up-regulation of bax and GADD45 mRNA levels. Short-term RF-EMF exposure for 6 h, but not for 48 h, resulted in a low and transient increase of DNA double strand breaks.
Paulraj and Behari [68]	Rat brain cells	Comet assay	Statistically significant ($p < 0.001$) increase in DNA single strand breaks in brain cells of rat.
Pavicic and Trosic [13]	V79 cells	Alteration of microtubule proteins	The microtubule structure altered after 3 h of irritation.
Phillips et al. [69]	Molt-4 T-lymphoblastoid cells	Comet assay	DNA damage decreased by (1) exposure to the iDEN signal (2.4 μW/g for 2 h or 21 h), (2) exposure to the TDMA signal (2.6 μW/g for 2 h and 21 h), (3) exposure to the TDMA signal (26 μW/g for 2 h), exposure to the iDEN signal (24 μW/g for 2 h) and 21 h significantly increased DNA damage.
Sarimov et al. [70]	Human blood lymphocytes	Chromatin condensation by anomalous viscosity	Analysis of pooled data from all donors showed statistically significant effect of 1-h exposure to MW. Effects differ at various GSM frequencies and vary between donors.
Sarkar et al. [71]	Mouse testis and brain cells	Restriction pattern after Hinfl treatment	As compared to control animals, band patterns in exposed animals were found to be distinctly altered in the range of 7–8 kb which was also substantiated by densitometric analysis.
Schwarz et al. [33]	Human cultured fibroblasts and lymphocytes	Alkaline comet assay and MN	UMTS exposure increased the CTF and induced centromere-negative micronuclei in human cultured fibroblasts in a dose- and time-dependent way. No UMTS effect was obtained with lymphocytes, either unstimulated or stimulated with phytohemagglutinin.
Sykes et al. [22]	pKZ1 mice	lacZ transgene inversion	No difference between the control and treated groups in the 1- and 5-day exposure groups, but a reduction in inversions below the spontaneous frequency in the 25-day exposure group. This suggests that RF radiation can lead to a perturbation in recombination frequency.
Tice et al. [72]	Human blood lymphocytes	Alkaline comet assay and MN	Exposure for either 3 or 24 h with the unmodulated signal did not induce a significant increase in DNA DSB or MN in lymphocytes. However, with the modulated signal there was a significant and reproducible increase in the frequency of micronucleated lymphocytes.
Tkalec et al. [14]	*Allium cepa* seeds	Germination, mitotic index, mitotic abnormalities	Increased mitotic aberrations in root meristematic cells of *A. cepa*. Effects were markedly dependent on the field frequencies applied as well as on field strength and modulation. Findings also indicate that mitotic effects of RF-EMF could be due to impairment of the mitotic spindle.
Trosic et al. [73]	Rat hematopoietic tissues	MN and polychromatic erythrocytes (PCEs)	The incidence of micronuclei/1000 PCEs in peripheral blood was significantly increased ($p < 0.05$) in the subgroup exposed to fro/MW radiation after eight irradiation treatments of 2 h each in comparison with the sham-exposed control group.

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Table 1 (*Continued*)

Reference	Biological system	Genotoxic endpoint	Results and comments
Trosic et al. [74]	Rat hematopoietic tissues	MN and polychromatic erythrocytes	In polychromatic erythrocytes significant differences ($p < 0.05$) for experimental days 8 and 15. The frequency of micronucleated PCEs was also significantly increased on experimental day 15 ($p < 0.05$).
Trosic and Busljeta [75]	Rat hematopoietic tissues and peripheral blood	MN and polychromatic erythrocytes	BMPCEs were increased on days 8 and 15, and PBPCEs were elevated on days 2 and 8 ($p < 0.05$).
Vijayalaxmi et al. [76]	C3H/HeJ cancer prone mice, peripheral blood and bone marrow	MN	No observed RF effects. A correction was published, stating that there was actually a significant MN increase in peripheral blood and bone marrow cells after chronic exposure to RF [Vijayalaxmi, M.R. Frei, S.J. Dusch, V. Guel, M.L. Meltz, J.R. Jauchem, Radiat. Res. 149 (3) (1998) 308].
Wu et al. [39]	Human epithelial lens cells	Comet assay and intracellular ROS	RF at 4 W/kg for 24 h significantly increased intracellular ROS and DNA damage. Both can be blocked completely by electromagnetic noise.
Yadav and Sharma [8]	Exfoliated buccal cells	MN in buccal cells	In exposed subjects 9.84 ± 0.745 micronucleated cells and 10.72 ± 0.889 total micronuclei (TMN) as compared to zero duration of exposure along with average 3.75 ± 0.774 MNC and 4.00 ± 0.808 TMN in controls. Correlation between 0–1, 1–2, 2–3 and 3–4 years of exposure and the frequency of MNC and TMN.
Yao et al. [40]	Human lens epithelial cells	Alkaline comet assay, gamma-H2AX foci, ROS level	SAR of 3 and 4 W/kg induced significant DNA damage in the comet assay, while no statistical difference in double strand breaks was found by γH2AX foci. Electromagnetic noise could block RF-induced ROS formation and DNA damage.
Yao et al. [41]	Human lens epithelial cells	Alkaline comet assay, γH2AX foci, ROS level	DNA damage was significantly increased by comet assay at 3 and 4 W/kg, whereas double strand breaks by γH2AX foci were significantly increased only at 4 W/kg. Significantly increased ROS levels were detected in the 3 and 4 W/kg groups.
Zhang et al. [77]	Chinese hamster lung cells (CHL)	γH2AX foci	Increased percentage of γH2AX foci positive cell of 1800 MHz RF EMF exposure for 24 h ($37.9 \pm 8.6\%$) or 2-acetylaminofluorene exposure ($50.9 \pm 9.4\%$). However, there was no significant difference between the sham-exposure and RF EMF exposure for 1 h ($31.8 \pm 8.7\%$).
Zotti-Martelli et al. [78]	Human blood lymphocytes	MN	Both spontaneous and induced MN frequencies varied in a highly significant way among donors ($p < 0.009$) and between experiments ($p < 0.002$), and a statistically significant increase of MN, although rather low, was observed dependent on exposure time ($p = 0.0004$) and applied power density ($p = 0.0166$).
Zotti-Martelli et al. [79]	Human blood lymphocytes	MN	The results showed for both radiation frequencies an induction of micronuclei as compared to the control cultures at a power density of 30 mW/cm^2 and after an exposure of 30 and 60 min.

Abbreviations: Mitomycin C (MMC), bleomycin (BLM), methylmethansulfonate (MMS), 4-nitroquinoline-1-oxide (4-NQ1O), ethylmethansulfonate (EMS), chromosomal aberration analysis (CA), micronucleus assay (MN), reactive oxygen species (ROS), and fluorescence *in vitro* hybridization (FISH).

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Table 2
Publications which do not report RF-EMF related genotoxic effects.

Reference	Biological system	Genotoxic endpoint	Results and comments
Antonopouloset al. [80]	Human blood lymphocytes	SCE	No increase in SCE or cell cycle progression found.
Belyaev et al. [81]	Rat brain, spleen, and thymus	Comet assay	GSM MWs at 915 MHz did not induce PFGE-detectable DNA double stranded breaks or changes in chromatin conformation, but affected expression of genes in rat brain cells.
Bisht et al. [82]	Mouse C3H 10T cells	MN	CDMA (3.2 or 4.8 W/kg) or FDMA (3.2 or 5.1 W/kg) RF-EMF radiation for 3, 8, 16 or 24 h did not result in a significant increase either in the percentage of binucleated cells with micronuclei or in the number of micronuclei per 100 binucleated cells.
Chang et al. [83]	*Escherichia coli* tester strain	Bacterial mutagenicity (Ames test)	No mutagenic or co-mutagenic effect with 4-NQ1O.
Ciaravino et al. [84]	CHO cells	SCE	Radiofrequency electromagnetic radiation (RF-EMF) did not change the number of SCEs that were induced by adriamycin.
Garson et al. [85]	Human blood lymphocytes	CA	No RF-EMF effect observed.
Gorlitz et al. [86]	B6C3F1 mice lymphocytes, erythrocytes, and keratinocytes	MN	No visible effect.
Gos et al. [87]	*Saccharomyces cerevisiae*	Mutation rates	No effects in fluctuation tests on forward mutation rates at CAN1, on the frequency of petite formation, on rates of intra-chromosomal deletion formation, or on rates of intra-genic recombination in the absence or presence of MMS.
Hook et al. [88]	Molt-4 T lymphoblastoid cells	Comet assay	No RF-EMF effects observed.
Juutilainen et al. [89]	Female CBA/S mice and K2 female transgenic mice	MN in erythrocytes	No effect on MN frequency.
Kerbacher et al. [90]	CHO cells	CA	No alteration was observed in the extent of chromosome aberrations induced by either simultaneous fro radiation exposure or convection heating to equivalent temperatures.
Komatsubara et al. [91]	Mouse m5S cells	CA	No effect on CA; temperature increase up to 41 °C at 100 W/kg.
Koyama et al. [92]	CHO cells	MN	No MN increase in cells exposed to HFEMF at a SAR of lower than 50 W/kg, while those at SARs of 100 and 200 W/kg were significantly higher when compared with the sham-exposed controls (temperature effect).
Lagroye et al. [93]	Rat brain cells	Alkaline comet assay	No observed effect.
Lagroye et al. [94]	C3H 10T1/2 cells	Comet assay, DNA–protein crosslinks	No observed effect.
Li et al. [95]	Murine C3H 10T cells	Comet assay	No observed effect.
Maes et al. [96]	Human blood lymphocytes	CA, SCE	Combined exposure of RF-EMF and to MMC and X-rays. Overall, no indication was found of a mutagenic, and/or co-mutagenic/synergistic effect.
Maes et al. [97]	Human blood lymphocytes	CA, SCE	Combined treatments with X-rays or MMC did not provide any indication of a synergistic action between the RF-EMF fields and X-rays or MMC.
Maes et al. [98]	Human blood lymphocytes	CA, SCE, Comet assay	The alkaline comet assay, SCE, and CA tests revealed no evidence of RF-EMF-induced genetic effects. No cooperative action was found between the electromagnetic field exposure and MMC using either the comet assay or SCE test.
Malyapa et al. [99]	Rat brain cells	Comet assay	No significant differences observed.
Malyapa et al. [100]	U87MG and C3H 10T1/2 cells	Comet assay	No significant differences observed.
Malyapa et al. [101]	U87MG and C3H 10T1/2 cells	Comet assay	No significant differences observed.
McNamee et al. [102]	Human blood lymphocytes	Comet assay and MN	No significant differences observed.
McNamee et al. [103]	Human blood lymphocytes	Comet assay and MN	No significant differences observed.
McNamee et al. [104]	Human blood lymphocytes	Comet assay	No significant differences observed.
Meltz et al. [105]	L5178Y mouse leukemic cells	Mutation in TK locus	No effect of RF-EMF alone or in the induced mutant frequency due to the simultaneous exposure to RF-EMF and proclaim, as compared with the proflavin exposures alone.
Ono et al. [106]	lacZ-transgenic mice	Mutations at the lac gene in spleen, liver, brain and testis	Mutation frequencies at the lacZ gene in spleen, liver, brain, and testis were similar to those observed in non-exposed mice.

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Table 2 (*Continued*)

Reference	Biological system	Genotoxic endpoint	Results and comments
Roti Roti et al. [107]	C3H 10T1/2 cells	Transformed foci	No statistically significant differences observed.
Sakuma et al. [108]	Human glioblastoma A172 cells and fetal lung fibroblasts	DNA strand breaks (comet assay?)	No statistically significant differences.
Scarfi et al. [109]	Human blood lymphocytes	MN	No statistically significant differences observed.
Speit et al. [24]	Human cultured fibroblasts	Comet assay and MN	No statistically significant differences observed.
Stronati et al. [110]	Human blood lymphocytes	Comet assay, CA, SCE, MN	By comparison with appropriate sham-exposed and control samples, no effect of RF-EMF alone could be found for any of the assay endpoints. In addition RF-EMF did not modify any measured effects of the X-radiation.
Takahashi et al. [111]	Big Blue mice brain tissues	lacZ transgene inversion	No statistically significant differences observed.
Verschaeve et al. [112]	Rat brain and liver tissues, erythrocytes	MN (erythrocytes) and comet assay	No genotoxic effect of RF-EMF alone. Co-exposures to MX and RF-EMF radiation did not significantly increase the response of blood, liver and brain cells compared to MX exposure only.
Vijayalaxmi et al. [113]	Human blood lymphocytes	CA and MN	No observed RF-EMF effects.
Vijayalaxmi et al. [114]	Human blood lymphocytes	CA and MN	No observed RF-EMF effects.
Vijayalaxmi et al. [115]	Human blood lymphocytes	Comet assay	No observed RF-EMF effects.
Vijayalaxmi et al. [116]	Human blood lymphocytes	CA, MN	No observed RF-EMF effects.
Vijayalaxmi et al. [117]	Rat hematopoietic tissues and erythrocytes	MN	No observed RF-EMF effects.
Vijayalaxmi et al. [118]	Rat whole body and head only exposures. BM erythrocytes	MN	No observed RF-EMF effects.
Vijayalaxmi et al. [119]	CF-1 male mice, peripheral blood and bone marrow	MN	No observed RF-EMF effects.
Zeni et al. [120]	Human blood lymphocytes	Comet assay, CA, SCE	No observed RF-EMF effects.
Zeni et al. [121]	Human blood lymphocytes	MN	No observed RF-EMF effects.

Abbreviations: Chromosomal aberration analysis (CA), methotrexat (MX), mitomycin C (MMC), 4-nitroqinoline-1-oxide (4-NQ1O), methylmethansulfonate (MMS), code division multiple access (CDMA), frequency division multiple access (FDMA), and time division multiple access (TDMA).

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Table 3
Publications which report synergistic RF-EMF effects in combination with other genotoxicants.

Reference	Genotoxic agents	Biological system	Genotoxic endpoint	Results and comments
Baohong et al. [122]	MMC, BLM, MMS, 4-NQ1O	Human blood lymphocytes	Alkaline comet assay	1.8 GHz RFR (SAR, 3 W/kg) for 2 h did not induce DSB, but could enhance the human lymphocyte DNA damage effects induced by MMC and 4-NQ1O. The synergistic DNA damage effects with BLM or MMS were not obvious.
Baohong et al. [123]	254 nm UVC	Human blood lymphocytes	Alkaline comet assay	RF exposure for 1.5 and 4 h did not enhance significantly human lymphocyte DNA damage, but could reduce and increase DNA damage of human lymphocytes induced by UVC at 1.5 and 4 h incubation respectively.
Kim et al. [124]	Cyclophosphamide, 4-NQ1O, EMS	L5178Y mouse lymphoma cells (comet assay) and CHL cells (CA)	Alkaline comet assay and CA	No direct cytogenetic effect of RF alone or in combination with cyclophosphamide or 4-NQ1O was found in the CA test and in the comet assay. However, RF had a potentiating effect in combination with cyclophosphamide or 4-NQ1O.
Maes et al. [125]	MMC	Human blood lymphocytes	SCE	Synergistic effect was observed with MMC.
Maes et al. [126]	MMC	Human blood lymphocytes	CA, SCE, comet assay	The combined exposure of the cells to the radiofrequency fields followed by their cultivation in the presence of mitomycin C revealed a very weak effect when compared to cells exposed to mitomycin C alone.
Manti et al. [11]	Previous 4 Gy X-ray radiation	Human blood lymphocytes	Chromosome aberration by FISH	No significant variations due to the UMTS exposure in the fraction of aberrant cells, but frequency of exchanges per cell in X-ray irradiated cells was significantly increased by UMTS at 2 W/kg.
Wang et al. [127]	254 nm UVC	Human blood lymphocytes	Comet assay	RF did not induce DNA damage but reduced or enhanced DNA damage by UVC at 1.5 or 4.0 h respectively.
Wang et al. [128]	MMC, BLM, MMS, 4-NQ1O	Human blood lymphocytes	Comet assay	RF did not induce DNA damage but enhanced DNA damage induced by MMC and 4-NQ1O.
Zhang et al. [129]	MMC	Human blood lymphocytes	Comet assay, micronucleus assay	No RF-induced DNA and chromosome damage, but increased MMC DNA damage by RF in comet assay.

Abbreviations: Mitomycin C (MMC), bleomycin (BLM), methylmethansulfonate (MMS), 4-nitroquinoline-1-oxide (4-NQ1O), ethylmethansulfonate (EMS), chromosomal aberration analysis (CA), fluorescence *in vitro* hybridization (FISH).

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fragments of chromosomes or from lagged chromosomes secondary to mitotic non-disjunction, the latter being detected by indirect immunofluorescence using kinetochore antibodies. Kinetochore-positive MN arise by epigenetic mechanisms (disturbances of the spindle apparatus). Kinetochore-negative MN arise from acentric chromosomal fragments. This is an important distinction, but has been performed in a few RF-EMF studies only, of which only one [12] reports an increase of kinetochore-positive MN albeit after a high SAR ≥ 78 W/kg. Two studies describe RF-EMF-induced disturbances of the spindle apparatus [13,14], and one reports an aneugenic RF-EMF effect on the basis of the size distribution of MN [15]. Of a total of 39 studies using the micronucleus assay 22 are MN-positive, and 17 MN-negative.

SCEs are analysed in metaphase chromosomes after two rounds of replication in the presence of 5-bromodeoxyuridine (BUDR). SCEs, which are induced during the S-phase of the cell cycle, represent an exchange between homologous chromatids, an event which by itself is genetically neutral. Nevertheless it is considered to reflect a recombinational repair of DNA double strand breaks (DSB), and may therefore serve as an indicator of genotoxic stress. Of 10 studies using SCE a GT(+) effect was reported in one only, 8 were negative, and one study reports RF-induced enhancement of genotoxicity by mitomycin C.

3. DNA fragmentation

The comet assay, also known as a "Single Cell Gel electrophoresis assay" (SCG), and the detection of gamma-H2AX foci are the most frequently used techniques to study RF-EMF-induced DNA strand breaks. The comet assay uses interphase nuclear DNA, which is unwinded under alkaline conditions and subsequently subjected to an electric field. Here DNA fragments migrate towards the anode, thereby forming a comet-like tail [16,17]. The alkaline comet assay detects DNA single strand as well as double strand breaks, but is not applicable in the presence of DNA crosslinking agents [18]. These breaks may occur not only by toxic influences but also by transcriptional and repair processes and by alkali-sensitive sites. Therefore this frequently used and very sensitive assay has a poor specificity. Of 41 studies using the comet assay 15 report comet-positive and 19 comet-negative results after RF-EMF exposure. RF-EMF enhancement of comet assay effects caused by other genotoxic agents is described in 7 studies.

Out of a multitude of DNA damage checkpoint proteins two have been used to detect DBS: H2AX, a member of the nuclear histone family [19], and P53 binding protein (53BP1). Both are rapidly phosphorylated only minutes after DNA damage and are then gathered in the vicinity of DNA double strand breaks. Here they form foci which can be visualized by indirect immunofluorescence [20,21]. These foci represent an initial and specific step in the repair process of exogenously induced DNA double strand breaks. It is important to realize, however, that repair processes of DSB are quantified, not DSB themselves. The method has been employed in 4 studies, predominantly using the yH2AX foci test. In all instances GT(+) effects have been detected.

DNA alterations have also been analysed by the anomalous viscosity time dependency test (AVTD, 1 GT(+) study), detecting conformational changes, and by quantitative PCR (QPCR, 1 GT(+) study) detecting structural changes in the DNA.

4. Gene mutations

In this category 6 studies have been performed using 4 different endpoints: (1) Altered restriction fragments (1 GT(+) study), (2) lacZ inversion in transgenic mice. This method has been used in 3 studies which all failed to detect an increased rate of inversions, but one found a reduced rate as compared to unexposed controls [22], which is interpreted as a RF-EMF-induced reduction of recombination repair. (3) Mutation at the thymidine kinase (TK) locus (1 negative study). (4) Bacterial his^- revertants (Ames test, 1 negative study).

5. Discussion

The large number of contradictory results among the 101 published studies on a genotoxic action of RF-EMF is tangling. Nevertheless patterns can be perceived. GT(+) as well as GT(−) findings have been reported at a standard absorption ratio (SAR) below 0.05 up to 100 W/kg and an exposure of 15 min and 48 h *in vitro*, and between hours and years *in vivo*. The outcome of studies was nearly independent from RF frequencies between 300 and 7700 MHz and the type of RF signal, either continuous wave (CW) or pulse-modulated (PM). GT(+) was obtained in 15 CW and 26 PM exposures, GT(−) in 14 CW and 27 PM exposures (some studies did not indicate the type of signal used). Contradictory results have been obtained even when two experienced groups performed the same experiments using the same cells and identical exposure conditions [23,24]. This may reflect a general problem of genotoxic studies being dependent on a multitude of factors which are difficult to control [25]. Some of the studies exploited here have shortcomings with respect to incompletely described or unreliable exposure conditions and/or an inadequate experimental design. Even a considerable publication bias in favour of negative results has been suspected (www.microwavenews.com/RR.html, 2006) [26].

The proportion of GT(+) effects is much higher *in vivo* (23/40) than i*n vitro* (29/77). (Since some studies have been performed on more than one biological system, the total number of GT(+) and GT(−) effects exceeds the total number of published studies.) Considering all genotoxic endpoints applied, the frequently used parameters chromosome analysis (9/21 GT(+)), comet assay (15/41 GT(+)), and sister-chromatid-exchange (1/10 GT(+)) showed the highest

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proportion of negative results, while the micronucleus assay yielded more positive than negative results (22/39 GT(+)). Since the SCE test which was negative in nearly all cases is known to be rather insensitive to radiomimetic (clastogenic) agents it can be speculated, that a clastogenic mechanism is involved in RF-EMF genotoxic action.

Epigenetic influences may also contribute to genotoxicity as demonstrated by RF-EMF-induced chromosomal non-disjunction and disturbances of the mitotic spindle. This is in agreement with the higher proportion of 22/39 GT(+) findings among studies using the micronucleus assay as compared to those using CA, because some of the micronuclei may represent lagged chromosomes. Epigenetic mechanisms may also be effective after a combined exposure to RF-EMF and various physical or chemical mutagens (Table 4). RF-EMF preferentially enhanced the genotoxic effect of 4-NQ1O (4/4), MMC (4/8), UVC (2/2), and cyclophosphamide (2/2). No synergistic effect was obtained using MMS and EMS (3/3), BLM (2/2), and adriamycine (2/2). Only one out of 3 studies reported a synergistic effect with X-rays.

Cells and tissues of different origin exhibit a clearly variable sensitivity for genotoxic RF-EMF effects (Table 4). This has also been observed with extremely low frequency (ELF)-EMF [27] and may be dependent on genetic differences [28]. GT(+) effects of RF-EMF were reported predominantly in the following biological systems: human lens epithelial cells (4/4), human buccal mucosa cells (2/2), rodent brain tissues (8/13), and rat hemopoietic tissues (5/7). GT(−) results have been obtained with mouse permanent cell lines (7/7) and permanent lymphoblastoid cells of various origin (7/7). This is in a striking analogy to RF-EMF-induced reduction of ornithine decarboxylase activity being detected in primary but not in secondary neural cells [29].

6. Proposed mechanisms of RF-EMF genotoxicity

Cells are unusually sensitive to electromagnetic fields [30]. Weak fields may accelerate electron transfer and thereby destabilize the H-bond of cellular macromolecules. This could explain the stimulation of transcription and protein expression, which has been observed after RF-EMF exposure [31,32]. However, the energy of weak EM fields is not sufficient directly to break a chemical bond in DNA. Therefore it can be concluded, that genotoxic effects are mediated by indirect mechanisms as microthermal processes, generation of oxygen radicals (ROS), or a disturbance of DNA-repair processes.

6.1. Thermal effects

An increase of temperature in the culture medium of RF-EMF exposed cells has been observed at very high SAR levels only [12]. The vast majority of GT(+) studies were conducted at SAR < 2.0 not leading to a detectable increase of temperature in the culture medium. Moreover, similar or larger effects have been observed at a 5′ on/10′ off intermittent exposure [23,33], a result that contradicts a

Table 4
Distribution RF-EMF effects in 101 published studies.

Biological system	RF-EMF effects		Synergistic effects	
	Positive	Negative	Positive	Negative
In vitro (all cells and tissues)	29	39	9	11
Human blood lymphocytes	18	23	8	4
Human lens epithelial cells	4			
Human cultured fibroblasts	2	2		
Human glioblastoma cells		3		
Human lymphoblastoid cells		2		
Mouse permanent cell lines		6		1
Mouse lymphoblastoid cells		1	1	1
Chinese hamster cells (CHO, V79)	4	2		3
E. coli		1		2
Yeast		1		
Rat granulosa cells	1			
In vivo (all species and tissues)	23	17	0	1
Human blood lymphocytes	4	2		
Human buccal mucosa cells	2			
Mouse sperm	1			
Mouse brain tissues	2			
Mouse polychromatic erythrocytes		4		
Rat brain tissues	6	4		1
Rat hemopoietic tissues	5	2		
Rat spleen, liver		2		
lacZ-transgenic mice		3		
Plants	2			
Cattle polychromatic erythrocytes	1			

Since several published studies have used more than 1 biological system the total of negative and positive effects exceeds the number of 101 publications.

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simple temperature-based mechanism of the observed genotoxic action. However, experimental results with microwave absorption at colloidal interfaces have demonstrated that the electric absorption of microwaves between 10 and 4000 MHz goes through a maximum with the size of bride droplets >100 and <10,000 nm, and depends on the type of ions and their concentrations [34]. This local absorption of microwaves may therefore lead to a considerable local heating in living cells during low energy microwave exposure.

6.2. Oxygen radicals

There is evidence that RF-EMF may stimulate the formation of reactive oxygen species in exposed cells *in vivo* [35–37] and *in vitro* [38–41]. Free oxygen radicals may form base adducts in DNA, the most important lesion being 8-OHdG, and oxidize also other cellular components, such as lipids leaving behind reactive species, that in turn can couple to DNA bases [42]. The first step in the generation of ROS by microwaves is mediated in the plasma membrane by NADH oxidase [43]. Subsequently ROS activates matrix metalloproteases (MMP), thereby initiating intracellular signalling cascades. It is interesting to note that these processes start within 5 min of radiation and at a very low field intensity of 0.005 W/cm^2. Moreover, higher effects have been obtained by intermittent radiation, when cells were left unirradiated for 10 min. This is in agreement with *in vitro* genotoxicity studies using the comet assay [23,33].

6.3. Alteration of DNA-repair processes

A considerable proportion of studies have investigated the consequences of a combined exposure to RF-EMF and various chemical or physical mutagens. 8/12 studies using human blood lymphocytes have demonstrated that RF-EMF enhanced the genotoxic action of other agents, preferentially of UV, MMC, or 4-NQ1O (an UV-mimetic agent). Since in all these experiments microwave exposure failed to induce detectable genotoxic effect by itself, an interference with DNA-repair mechanisms has been postulated, however, there is no direct experimental proof yet. An alteration of recombinational repair has also been proposed by Sykes et al. [22] as an explanation of the reduced rate of inversions in lacZ-transgenic mice after RF-EMF treatment.

An influence of microwave exposure on DNA-repair processes has long been proposed for power frequency electromagnetic fields [35]. A recent epidemiological investigation into the frequency of polymorphisms of DNA-repair genes in children with acute leukemia living in the vicinity of power line transformers [44] emphasizes the significance DNA-repair impairment for an EMF related increase of this malignancy. There was a significant gene–environment interaction (COR = 4.31) between the electromagnetic field intensities and a less active genetic variant of XRCC1, a crucial enzyme in base excision repair.

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Epidemiological evidence for an association between use of wireless phones and tumor diseases

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Abstract

During recent years there has been increasing public concern on potential cancer risks from microwave emissions from wireless phones. We evaluated the scientific evidence for long-term mobile phone use and the association with certain tumors in case–control studies, mostly from the Hardell group in Sweden and the Interphone study group. Regarding brain tumors the meta-analysis yielded for glioma odds ratio (OR) = 1.0, 95% confidence interval (CI) = 0.9–1.1. OR increased to 1.3, 95% CI = 1.1–1.6 with 10 year latency period, with highest risk for ipsilateral exposure (same side as the tumor localisation), OR = 1.9, 95% CI = 1.4–2.4, lower for contralateral exposure (opposite side) OR = 1.2, 95% CI = 0.9–1.7. Regarding acoustic neuroma OR = 1.0, 95% CI = 0.8–1.1 was calculated increasing to OR = 1.3, 95% CI = 0.97–1.9 with 10 year latency period. For ipsilateral exposure OR = 1.6, 95% CI = 1.1–2.4, and for contralateral exposure OR = 1.2, 95% CI = 0.8–1.9 were found. Regarding meningioma no consistent pattern of an increased risk was found. Concerning age, highest risk was found in the age group <20 years at time of first use of wireless phones in the studies from the Hardell group. For salivary gland tumors, non-Hodgkin lymphoma and testicular cancer no consistent pattern of an association with use of wireless phones was found. One study on uveal melanoma yielded for probable/certain mobile phone use OR = 4.2, 95% CI = 1.2–14.5. One study on intratemporal facial nerve tumor was not possible to evaluate due to methodological shortcomings. In summary our review yielded a consistent pattern of an increased risk for glioma and acoustic neuroma after >10 year mobile phone use. We conclude that current standard for exposure to microwaves during mobile phone use is not safe for long-term exposure and needs to be revised.
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Keywords: Brain tumors; Glioma; Acoustic neuroma; Meningioma; Cellular phones; Cordless phones

1. Introduction

During the last decade there has been a rapid development of wireless technology and along with that an increased use of wireless telephone communication in the world. Most persons use mobile phones and cordless phones. Additionally most populations are exposed to radiofrequency/microwave (RF) radiation emissions from wireless devices such as cellular antennas and towers, broadcast transmission towers, voice and data transmission for cell phones, pagers and personal digital assistants and other sources of RF radiation.

Concerns of health risks have been raised, primarily an increased risk for brain tumors, since the brain is the near field target organ for microwave exposure during mobile phone calls. Especially the ipsilateral brain (same side as the mobile phone has been used) is exposed, whereas the contralateral side (opposite side to the mobile phone) is much less exposed [1]. Thus, for risk analysis it is of vital importance to have information on the localisation of the tumor in the brain and which side of the head that has been predominantly used during phone calls.

Since Sweden was one of the first countries in the world to adopt this wireless technology a brief history is given in the following. First, analogue phones (NMT; Nordic Mobile Telephone System) were introduced on the market in the early 1980s using both 450 and 900 Megahertz (MHz) carrier waves. NMT 450 was used in Sweden since 1981 but closed down in December 31, 2007, whereas NMT 900 operated during 1986–2000.

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Table 1
Odds ratios (ORs) and 95% confidence intervals (CIs) from 11 case–control studies on glioma including meta-analysis of the studies. Numbers of exposed cases and controls are given.

Author, year of publication, country, reference number	No. of cases	No. of controls	OR	95% CI
Inskip et al., 2001, USA [23]	201	358	1.0	0.7–1.4
Auvinen et al., 2002, Finland [24]	Not given	Not given	1.5	1.0–2.4
Lönn et al., 2005, Sweden [25][a]	214	399	0.8	0.6–1.0
Christensen et al., 2005, low-grade glioma, Denmark [26][a]	47	90	1.1	0.6–2.0
Christensen et al., 2005, high-grade glioma, Denmark [26][a]	59	155	0.6	0.4–0.9
Hepworth et al., 2006, UK [27][a]	508	898	0.9	0.8–1.1
Schüz et al., 2006, Germany [28]	138	283	1.0	0.7–1.3
Hardell et al., 2006, Sweden [12], all glioma	346	900	1.4	1.1–1.7
Low-grade glioma	65	900	1.4	0.9–2.3
High-grade glioma	281	900	1.4	1.1–1.8
Lahkola et al., 2006, Denmark, Norway, Finland, Sweden, UK [29]	867	1 853	0.8	0.7–0.9
Hours et al., 2007, France [30]	59	54	1.2	0.7–2.1
Klaeboe et al., 2007, Norway [31][a]	161	227	0.6	0.4–0.9
Takebayashi et al., 2008, Japan [17]	56	106	1.2	0.6–2.4
Meta-analysis	>1667[b]	>3554[b]	1.0	0.9–1.1

[a] Not included in meta-analysis because already part of pooled data in Lahkola et al., 2006 [29].
[b] Total number could not be calculated since numbers were not presented in one publication [24].

The digital system (GSM; Global System for Mobile Communication) using dual band, 900 and 1800 MHz, started to operate in 1991 and now dominates the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1900 MHz RF broad band transmission has been introduced worldwide since a few years, in Sweden since 2003.

Desktop cordless phones have been used in Sweden since 1988, first analogue 800–900 MHz RF fields, but since early 1990s the digital 1900 MHz DECT (Digital Enhanced Cordless Telecommunications) system is used. In our studies on tumor risk associated with use of wireless phones, we have also assessed use of cordless phones. However, most other research groups have not published such data at all, or only in a scanty way, so exposure to RF from DECT is not further discussed here. Instead the reader is referred to our previous publications on this issue [2–13].

The initial studies on brain tumor risk had too short latency periods to give a meaningful interpretation. However, during recent years studies have been published that enable evaluation of ≥10-years latency period risk, although still mostly based on low numbers [14,15]. A ≥10-years latency period seems to be a reasonable minimum period to indicate long-term carcinogenic risks from exposure to RF fields during use of mobile or cordless phones.

Table 2
Odds ratios (ORs) and 95% confidence intervals (CIs) from six case–control studies on glioma including meta-analysis of the studies using ≥10 year latency period. Numbers of exposed cases and controls are given.

Study	Total			Ipsilateral			Contralateral		
Author, year of publication, country, latency, reference number	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI
Lönn et al., 2005, Sweden, ≥10 years [25][a]	25/38	0.9	0.5–1.5	15/18	1.6	0.8–3.4	11/25	0.7	0.3–1.5
Christensen et al., 2005, Denmark, low-grade glioma, ≥10 years [26][a]	6/9	1.6	0.4–6.1	–	–	–	–	–	–
Christensen et al., 2005, Denmark, high-grade glioma, ≥10 years [26][a]	8/22	0.5	0.2–1.3	–	–	–	–	–	–
Hepworth et al., 2006, UK, ≥10 years [27][a]	66/112	0.9	0.6–1.3	Not given	1.6	0.9–2.8	Not given	0.8	0.4–1.4
Schüz et al., 2006, Germany, ≥10 years [28]	12/11	2.2	0.9–5.1	–	–	–	–	–	–
Hardell et al., 2006, Sweden, >10 years [12], all glioma	78/99	2.7	1.8–3.9	41/28	4.4	2.5–7.6	26/29	2.8	1.5–5.1
Low-grade glioma	7/99	1.5	0.6–3.8	2/28	1.2	0.3–5.8	4/29	2.1	0.6–7.6
High-grade glioma	71/99	3.1	2.0–4.6	39/28	5.4	3.0–9.6	22/29	3.1	1.6–5.9
Lahkola et al., 2006, Denmark, Norway, Finland, Sweden, UK, ≥10 years [29]	143/220	0.95	0.7–1.2	77/117	1.4	1.01–1.9	67/121	1.0	0.7–1.4
Meta-analysis	233/330	1.3	1.1–1.6	118/145	1.9	1.4–2.4	93/150	1.2	0.9–1.7

[a] Not included in meta-analysis because already part of pooled data in Lahkola et al., 2006 [29].

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Table 3
Odds ratios (ORs) and 95% confidence intervals (CIs) from nine case–control studies on acoustic neuroma including meta-analysis of the studies. Numbers of exposed cases and controls are given.

Author, year of publication, country, reference number	No. of cases	No. of controls	OR	95% CI
Inskip et al., 2001, USA [23]	40	358	0.8	0.5–1.4
Lönn et al., 2004, Sweden [32][a]	89	356	1.0	0.6–1.5
Christensen et al., 2004, Denmark [33][a]	45	97	0.9	0.5–1.6
Schoemaker et al., 2005, Denmark, Finland, Sweden, Norway, Scotland, England [34]	360	1934	0.9	0.7–1.1
Hardell et al., 2006, Sweden [11]	130	900	1.7	1.2–2.3
Takebayashi et al., 2006, Japan [35]	51	192	0.7	0.4–1.2
Klaeboe et al., 2007, Norway [31][a]	22	227	0.5	0.2–1.0
Schlehofer et al., 2007, Germany [36]	29	74	0.7	0.4–1.2
Hours et al., 2007, France [30]	58	123	0.9	0.5–1.6
Meta-analysis	668	3581	1.0	0.8–1.1

[a] Not included in meta-analysis because already part of pooled data in Schoemaker et al., 2005 [34].

Long-term exposure to RF fields from mobile phones and brain tumor risk is of importance to evaluate, not the least since the use of cellular phones is globally widespread with high prevalence among almost all age groups in the population. In the following we discuss mobile phone use and the association with brain tumors, but also other tumor types that have been studied. Recently, we published a detailed review of studies on brain tumors [14] followed by meta-analyses of published studies regarding glioma, acoustic neuroma and meningioma [15]. We have now recalculated these results with the addition of two new recently published articles from the Interphone study group [16,17]. Studies from individual countries were only included in the meta-analyses if they were not also included in the joint publications for several countries. For odds ratio (OR) and 95% confidence interval (CI) we used fixed effects model as in the recent publication by Kundi [18]. The analyses were done using Stata/SE 10 (Stata/SE 10 for Windows; StataCorp., College Station, TX).

One case–control study was excluded since no separate data were presented for glioma, acoustic neuroma or meningioma [19], and another since no overall data on acoustic neuroma were published, only for some time periods without results for ≥10 year latency period [20].

Due to several methodological limitations a Danish cohort study on "mobile phone subscribers" [21] is not possible to include in the meta-analysis, and the same methodological shortcomings prevail in the published updated cohort [22]. In the following only a short overview of the results for brain tumors is given, since we have discussed these issues in more detail elsewhere [14,15]. The other tumor types that have been studied are salivary gland tumors, non-Hodgkin lymphoma (NHL), testicular cancer, eye melanoma and facial nerve tumor.

2. Glioma

Glioma is a malignant type of brain tumor and comprises about 60% of all central nervous system tumors. The highly malignant glioblastoma multiform, with poor survival, is included in this group.

Eleven case–control studies present results for glioma [12,17,23–31]. Of these eight [17,25–31] were part of the Interphone study and four of these [25–27,31] were included in a pooled-analysis with additional data for Finland [29]. The results are presented in Table 1. Overall no decreased

Table 4
Odds ratios (ORs) and 95% confidence intervals (CIs) from four case–control studies on acoustic neuroma including meta-analysis of the studies using ≥10 year latency period. Numbers of exposed cases and controls are given.

Study	Total			Ipsilateral			Contralateral		
Author, year of publication, country, latency, reference number	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI
Lönn et al., 2004, Sweden, ≥10 years [32][a]	14/29	1.8	0.8–4.3	12/15	3.9	1.6–9.5	4/17	0.8	0.2–2.9
Christensen et al., 2004, Denmark, ≥10 years [33][a]	2/15	0.2	0.04–1.1	–	–	–	–	–	–
Schoemaker et al., 2005, Denmark, Finland, Sweden, Norway, Scotland, England, ≥10 years [34]	47/212	1.0	0.7–1.5	31/124	1.3	0.8–2.0	20/105	1.0	0.6–1.7
Hardell et al., 2006, Sweden, >10 years [11]	20/99	2.9	1.6–5.5	10/28	3.5	1.5–7.8	6/29	2.4	0.9–6.3
Meta-analysis	67/311	1.3	0.97–1.9	41/152	1.6	1.1–2.4	26/134	1.2	0.8–1.9

[a] Not included in meta-analysis because already part of pooled data in Schoemaker et al., 2005 [34].

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or increased risk was found for glioma in the meta-analysis; OR = 1.0, 95% CI = 0.9–1.1.

Results for 10 year latency period are presented in Table 2. Six studies [12,25–29] gave such information and three [25–27] of these were also part of the publication by Lahkola et al. [29]. The meta-analysis yielded significantly increased risk for glioma with OR = 1.3, 95% CI = 1.1–1.6 increasing to OR = 1.9, 95% CI = 1.4–2.4 for ipsilateral exposure. The latter results were based on 118 exposed cases and 145 exposed controls. Regarding contralateral exposure to microwaves from mobile phones a lower risk was calculated, OR = 1.2, 95% CI = 0.9–1.7 (n = 93 cases, 150 controls). It should be noted that in the study by Takebayashi et al. [17] analyses of maximum microwave energy absorbed at the location of the tumor gave OR = 1.6, 95% CI = 0.6–4.2 related to the highest quartile of cumulative phone time weighted by maxSAR and OR = 5.8, 95% CI = 0.96–36 for subjects with cumulative maxSAR-hour of ≥10 W/kg-h.

3. Acoustic neuroma

These tumors are benign and do not undergo malignant transformation. They tend to be encapsulated and grow in relation to the auditory and vestibular portions of nerve VIII. They are slow growing tumors initially in the auditory canal, but gradually grow out into the cerebellopontine angle, where they come into contact with vital brain stem centers.

Nine case–control studies have been published [11,23, 30–36], see Table 3. Seven [30–36] were part of the Interphone study and three [31–33] were included in the publication by Schoemaker et al. [34]. Analysis of the total material yielded OR = 1.0, 95% CI = 0.8–1.1 increasing to 1.3, 95% CI = 0.97–1.9 using 10 year latency period, Table 4. For ipsilateral exposure OR increased further to 1.6, 95% CI = 1.1–2.4, whereas contralateral exposure gave a non-significantly increased risk, OR = 1.2, 95% CI = 0.8–1.9.

4. Meningioma

Meningioma arises from the pia or archnoid, which are the covering layers of the central nervous system. The majority are benign tumors that are encapsulated and well-demarched from surrounding tissue.

Regarding meningioma results have been published from nine case–control studies, Table 5 [11,16,17,23,25,26, 28,30,31]. Of these, seven [16,17,25,26,28,30,31] were part of the Interphone studies. The Lahkola et al. study [16] included three separately published Interphone studies [25,26,31]. The meta-analysis in Table 5 gave a significantly reduced OR = 0.9, 95% CI = 0.8–0.9. These results were mainly caused by the findings in the Interphone study [16] with the largest numbers of cases and controls yielding OR = 0.8, 95% CI = 0.7–0.9 in that study.

Using 10 year latency period OR was close to unity and somewhat increased for ipsilateral exposure, OR = 1.3, 95% CI = 0.9–1.8, Table 6. Regarding contralateral exposure OR was non-significantly decreased to 0.8, 95% CI = 0.5–1.3. The results for laterality were based on only two studies [11,16].

5. Brain tumor risk in different age groups

We grouped cases and controls according to age when they started to use a mobile or a cordless phone [11,12]. Consistently we found the highest risk for those with first use <20 years age. Thus, for malignant brain tumors OR = 2.7, 95% CI = 1.3–6.0 was calculated for mobile phones and OR = 2.1, 95% CI = 0.97–4.6 for cordless phones. The corresponding results for benign brain tumors were OR = 2.5, 95% CI = 1.1–5.9 and OR = 0.6, 95% CI = 0.2–1.9, respectively. Previously, we published results for diagnosis of brain tumor in different age groups [37] and found highest OR = 5.9, 95% CI = 0.6–55 for ipsilateral use of analogue phones in the youngest age group 20–29 years at the time of diagnosis. Using a >5 years latency period increased the risk further.

6. Brain tumor risk for use of mobile phone in urban and rural areas

There is a difference in output power of digital mobile phones between urban and rural areas. Adaptive power control (APC) regulates power depending on the quality of the transmission. In rural areas with on average longer distance to the base station the output power level is higher than in urban areas with dense population and shorter distance to the base stations. We studied the risk for brain tumors in urban versus rural living from the data in our study with cases diagnosed January 1, 1997 to June 30, 2000 [38]. Regarding digital phones OR = 1.4, 95% CI = 0.98–2.0 was obtained for living in rural areas increasing to OR = 3.2, 95% CI = 1.2–8.4 with >5 years latency period. The corresponding results for living in urban areas were OR = 0.9, 95% CI = 0.8–1.2 and OR = 0.9, 95% CI = 0.6–1.4, respectively.

7. Salivary gland tumors

The salivary glands, especially the parotid gland, are targets for near-field microwave exposure during calls with wireless phones. A Finnish study reported OR = 1.3, 95% CI = 0.4–4.7 for those who had ever had a mobile phone subscription [24].

Results from three case–control studies have been published, one from Sweden, one from the Nordic countries and one from Israel. During the same period as our studies on brain tumors we performed a study on salivary gland tumors [39]. Our study included the whole Swedish pop-

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Table 5
Odds ratios (ORs) and 95% confidence intervals (CIs) from nine case–control studies on meningioma including meta-analysis of the studies. Numbers of exposed cases and controls are given.

Author, year of publication, country, reference number	No. of cases	No. of controls	OR	95% CI
Inskip et al., 2001 (USA) [23]	67	358	0.8	0.5–1.2
Lönn et al., 2005 (Sweden) [25][a]	118	399	0.7	0.5–0.9
Christensen et al., 2005 (Denmark) [26][a]	67	133	0.8	0.5–1.3
Schüz et al., 2006 (Germany) [28]	104	234	0.8	0.6–1.1
Hardell et al., 2006 (Sweden) [11]	347	900	1.1	0.9–1.3
Klaeboe et al., 2007 (Norway) [31][a]	96	227	0.8	0.5–1.1
Hours et al., 2007 (France) [30]	71	80	0.7	0.4–1.3
Lahkola et al., 2008 (Denmark, Norway, Finland, Sweden, UK) [16]	573	1696	0.8	0.7–0.9
Takebayashi et al., 2008, Japan [17]	55	118	0.7	0.4–1.2
Meta-analysis	1217	3386	0.9	0.8–0.9

[a] Not included in meta-analysis because already part of pooled data in Lahkola et al., 2008 [16].

ulation. Cases were recruited by using the regional cancer registries, and most had a malignant disease. They were diagnosed during 1994–2000, but with some variation for the different medical regions in Sweden. Population based controls were used as reference group. The questionnaire was answered by 267 (91%) of the cases and 750 (92%) of the controls. Of the cases 245 had a cancer diagnosis. Overall no association was found; analogue phones yielded OR = 0.9, 95% CI = 0.6–1.4, digital OR = 1.0, 95% CI = 0.7–1.5 and cordless phones OR = 1.0, 95% CI = 0.7–1.4. No effect of tumor induction period was found, although regarding >10 year latency period only 6 cases had used an analogue phone, OR = 0.7, 95% CI = 0.3–1.7, whereas no case had used a digital or cordless phone with that latency period. The results did not change significantly for ipsilateral or contralateral tumors.

The Nordic part of the Interphone case–control study of an association between use of mobile phones and parotid gland tumors was published in 2006 [40]. Detailed information about mobile phone use was obtained from 60 (85%) cases with malignant tumor, 112 (88%) with benign tumor and 681 (70%) controls. Regular mobile phone use gave OR = 0.7, 95% CI = 0.4–1.3 for malignant tumors and OR = 0.9, 95% CI = 0.5–1.5 for benign parotid gland tumors. For ipsilateral mobile phone use a latency period of ≥10 year yielded OR 0.7, 95% CI = 0.1–5.7 for malignant tumors ($n = 1$) and OR = 2.6, 95% CI = 0.9–7.9 for benign tumors ($n = 6$). Contralateral use was reported by one case with benign tumor and no case with malignant tumor in the same latency group.

As part of the Interphone study results on parotid gland tumor were reported from Israel [41]. It included 402 benign and 58 malignant incident cases, total 460 (87%) of 531 eligible for the time period 2001–2003. Population based matched controls were used, in total 1266 (66%) out of 1920 eligible subjects. Thirteen cases had a latency period of ≥10 year, which gave OR = 0.9, 95% CI = 0.4–1.8. No significantly increased risk was found for duration of use; ≥10 year yielded OR = 1.0, 95% CI = 0.5–2.1. However, for cumulative number of calls >5479 OR = 1.6, 95% CI = 1.1–2.2 was found for ipsilateral and both ears used equally, whereas contralateral use gave OR = 0.8, 95% CI = 0.5–1.2. Similarly, cumulative call time >266.3 h yielded OR = 1.5, 95% CI = 1.1–2.1; contralateral use gave OR = 0.8, 95% CI = 0.6–1.3.

In the meta-analysis using 10 year latency period no overall increased risk was found, OR = 0.8, 95% CI = 0.5–1.4, but for ipsilateral use it increased to OR = 1.7, 95% CI = 0.96–2.9, whereas contralateral use gave OR = 0.4, 95% CI = 0.2–1.2, Table 7.

Table 6
Odds ratios (ORs) and 95% confidence intervals (CIs) from five case–control studies on meningioma including meta-analysis of the studies using ≥10 year latency period. Numbers of exposed cases and controls are given.

Study	Total			Ipsilateral			Contralateral		
Author, year of publication, country, latency, reference number	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI
Lönn et al., 2005, Sweden, ≥10 years [25][a]	12/36	0.9	0.4–1.9	5/18	1.3	0.5–3.9	3/23	0.5	0.1–1.7
Christensen et al., 2005, Denmark, ≥10 years [26][a]	6/8	1.0	0.3–3.2	–	–	–	–	–	–
Schüz et al., 2006, Germany, ≥10 years [28]	5/9	1.1	0.4–3.4	–	–	–	–	–	–
Hardell et al., 2006, Sweden, >10 years [11]	38/99	1.5	0.98–2.4	15/28	2.0	0.98–3.9	12/29	1.6	0.7–3.3
Lahkola et al., 2008 (Denmark, Norway, Finland, Sweden, UK) [16]	73/212	0.9	0.7–1.3	33/113	1.1	0.7–1.7	24/117	0.6	0.4–1.03
Meta-analysis	116/320	1.1	0.8–1.4	48/141	1.3	0.9–1.8	36/146	0.8	0.5–1.3

[a] Not included in meta-analysis because already part of pooled data in Lahkola et al., 2008 [16].

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Table 7
Odds ratios (ORs) and 95% confidence intervals (CIs) from three case–control studies on salivary gland tumors including meta-analysis of the studies using ≥10 year latency period.

Study	Total			Ipsilateral			Contralateral		
Author, year of publication, country, latency, reference number	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI
Hardell et al., 2004, Sweden, >10 years [39]	6/35	0.7	0.3–1.7	5/13	1.5	0.5–4.2	1/15	0.3	0.03–2.1
Lönn et al., 2006, malignant, Sweden, ≥10 years [40]	2/36	0.4	0.1–2.6	1/23	0.7	0.1–5.7	0/19	–[a]	–[a]
Lönn et al., 2006, benign, Sweden, ≥10 years [40]	7/15	1.4	0.5–3.9	6/9	2.6	0.9–7.9	1/9	0.3	0.0–2.3
Sadetzki et al., 2007, Israel, ≥10 years [41]	13/26	0.9	0.4–1.8	10/16	1.6	0.7–3.7	3/10	0.6	0.2–2.3
Meta-analysis	28/112	0.8	0.5–1.4	22/61	1.7	0.96–2.9	5/34	0.4	0.2–1.2

[a] Not included in meta-analysis because OR could not be estimated.

8. Non-Hodgkin lymphoma

The incidence of NHL increased since the 1960s in Sweden as well as in many western countries with reliable cancer registries. This trend has levelled off since the 1990s, and decreasing exposure to environmental contaminants such as PCBs and dioxins, and also certain pesticides has been postulated to be one explanation [42,43]. As part of a large case–control study on NHL, mainly on exposure to pesticides [44], also questions on the use of wireless phones were included. The study covered the time period December 1, 1999 to April 30, 2002. The questionnaire was answered by 910 (91%) cases and 1016 (92% controls). The majority of the cases had B-cell NHL and we did not find any association with use of wireless phones [45]. Regarding T-cell NHL ($n = 53$) we observed somewhat increased risks; use of analogue phone gave OR = 1.5, 95% CI = 0.6–3.7, digital phone OR = 1.9, 95% CI = 0.8–4.8 and cordless phone OR = 2.5, 95% CI = 1.1–5.6. For certain subtypes of T-cell NHL, the cutaneous and leukemia types, the risks increased further for analogue phone to OR = 3.4, 95% CI = 0.8–15, digital phone to OR = 6.1, 95% CI = 1.3–30, and cordless phone to OR = 5.5, 95% CI = 1.3–24. These results were, however, based on low numbers.

A study from USA included 551 NHL cases and 462 frequency matched controls [46]. Among regular mobile phone users NHL risk was not significantly associated with minutes per week, duration, cumulative lifetime or years of first use. However, total time >8 years gave OR = 1.6, 95% CI = 0.7–3.8. The risk increased with number of years, and was significant for the not specified group of NHL after ≥6 years use yielding OR = 3.2, 95% CI = 1.2–8.4.

9. Testicular cancer

An increasing incidence of testicular cancer has been noted in most western countries during the recent decades. It is the most common cancer type in young men and is not regarded to be an occupational disease. Cryptorchidism is an established risk factors, but also perinatal exposure to persistent organic pollutants with hormone activity has been suggested to be another risk factor [47,48]. There has been concern in the population that use of mobile phones might be a risk factor for testicular dysfunction. We performed a case–control study mainly on the use of PVC plastics as risk factor for testicular cancer [49], and included in the questionnaire also questions on the use of wireless phones. The results were based on answers from 542 (92%) cases with seminoma, 346 (89%) with non-seminoma and 870 (89%) controls [50]. Overall no association was found [50]. Only 13 cases with seminoma had used an analogue phone >10 years yielding OR = 2.1, 95% CI = 0.8–5.1 and one case with non-seminoma; OR = 0.3, 95% CI = 0.04–2.6. No case had used a digital or cordless phone with latency period >10 years. OR did not increase with cumulative use in hours for the different phone types. Regarding use of mobile phone in the stand by mode border line significance was found for seminoma, OR = 1.3, 95% CI = 1.03–1.7, but not for non-seminoma; OR = 0.9, 95% CI = 0.7–1.3. For different localisations during stand by, highest risk was found for seminoma for keeping the phone in ipsilateral trousers pocket, OR = 1.8, 95% CI = 0.97–3.4 whereas contralateral pocket gave OR = 1.0, 95% CI = 0.5–2.0.

10. Malignant melanoma of the eye

Stang et al. [51] conducted a hospital- and population-based case–control study of uveal melanoma and occupational exposures to different sources of radiofrequency radiation. A total of 118 cases with uveal melanoma and 475 controls were included. Exposure to RF-transmitting devices was rated as (a) no RF exposure, (b) possible exposure to mobile phones, or (c) probable/certain exposure to mobile phones. An elevated risk for exposure to RF-transmitting devices was reported. Exposure to radio sets gave OR = 3.0, 95% CI = 1.4–6.3 and probable/certain exposure to mobile

phones OR = 4.2, 95% CI = 1.2–14.5. The authors concluded that several methodologic limitations prevented their results from providing clear evidence on the hypothesized association.

The study was commented among others Johansen et al. [52]. In their cohort of mobile phone subscribers in Denmark no support for an association between mobile phones and ocular melanoma was found. However, as discussed elsewhere [14,15,18,55], there are several methodological limitations in the Danish cohort [21,22] that hamper the interpretation of their findings.

The paper by Stang et al. [51] has also been commented by Inskip [53] in an editorial, the main point being that missing from the paper is any consideration of occupational or recreational exposure to UV radiation.

11. Intratemporal facial nerve tumor

So far only one investigation has studied the risk of intratemporal facial nerve (IFN) tumor and the use of mobile phone [54]. A case–control approach was used with 18 patients with IFN tumors matched with controls ($n = 192$) treated for other diseases, 51 patients treated for acoustic neuroma, 72 treated for rhinosinusitis, and 69 for dysphonia and gastroesophageal reflux. Risk of facial nerve tumorigenesis was compared by extent of mobile phone use. The OR of developing an IFN tumor was 0.6, 95% CI = 0.2–1.9 with any handheld mobile phone use and OR = 0.4, 95% CI = 0.1–2.1 for regular mobile phone use. However, they concluded that the short duration of use precludes definite exclusion as a risk for IFN tumor development. Certainly the cases were too few for a sound epidemiological study and it was not correct to include patients with acoustic neuroma in the reference group.

12. Discussion

A review on use of mobile phones and the association with brain tumors included all case–control studies that we have identified in the peer-review literature. Most studies have published data with rather short latency period and limited information on long-term users.

No other studies than from the Hardell group has published comprehensive results for use of cordless phones (DECT) [2–15]. As we have discussed in our publications it is pertinent to include also such use in this type of studies. Cordless phones are an important source of exposure to microwaves and they are usually used for a longer time period on daily basis as compared to mobile phones. Thus, to exclude such use, as was done in e.g. the Interphone studies, could lead to an underestimation of the risk for brain tumors from use of wireless phones.

We have discussed shortcomings in the Interphone studies in detail elsewhere [55]. Regarding glioma the Swedish Interphone study reported 23 ORs in Table 2 in that publication [25] and 22 of these were <1.0 and one OR = 1.0. For meningioma all 23 ORs were <1.0, six even significantly so. These results indicate a systematic bias in the study unless use of mobile phones prevents glioma and meningioma, which is biologically unlikely. It should be noted that several of the overall ORs also in other Interphone studies were <1.0, some even significantly so. As an example, in the Danish Interphone study on glioma [26] all 17 ORs for high-grade glioma were <1.0, four significantly decreased. Also other Interphone studies reported ORs significantly <1.0, that is a protective effect or rather systematic bias in the studies [16,29,31].

Use of cellular telephones was mostly assessed by personal interviews in the Interphone studies. It is not described how these personal interviews were organized, a tremendous task considering that vast parts of Sweden from north to south had to be covered. In the sparsely populated and extended area in northern Sweden personal interviews must have meant lots of long distance traveling and imposed additional stress on the interviewers. No information was given in the articles on how or if this methodological problem was solved, for example were controls only included from more densely populated areas.

The interviews in the Interphone study were extensive and computer aided. It is likely that such an interview creates a stressful situation for a patient with a recent brain tumor diagnosis and operation. These patients, especially under pressure with a newly diagnosed brain tumor and possible surgery, often have difficulties remembering past exposures and inevitably have problems with concentration and may have problems with other cognitive shortcomings. In the Danish part of the Interphone study it was concluded that the patients scored significantly lower than controls due to recalling words (aphasia), problems with writing and drawing due to paralysis [26]. According to our experience a better option would have been to start with a mailed questionnaire, that can be answered by the patient during a period of more well-being, if necessary this can be complemented by a telephone interview. After surgery it is easier to answer a questionnaire at home, also with the possibility to check phone bills to verify the use. This procedure has the additional advantage that it can be accomplished without disclosure during the data collection, whether a person is a case or a control. Certainly, knowing if it was a case or a control that was interviewed in the Interphone study may have introduced observational bias.

It has been argued that recall bias might be introduced in case–control studies on cancer patients, since the patients would be more prone to find a cause for their disease than the controls. However, the contrary is often the situation since patients do not want to blame themselves for their disease. In one article we presented data on the patients own assumptions of causes of their brain tumor [5]. Of 1429 cases only two expressed concern about mobile phones and no about cordless

phones. Interestingly, cases with a previous cancer diagnosis reported lower frequency for use of wireless phones than those with no previous cancer. No interviewer bias could be demonstrated when exposure data in the questionnaire were compared before and after phone interviews [5].

The diagnosis of tumor type as well as grading is based on histopathology. X-ray investigation or MR alone is insufficient. Of the 371 cases with glioma in the Swedish Interphone study [25] histopathology examination of the tumor was available for 328 (88%) cases, and for 225 (82%) of the meningioma cases. Thus, it is possible that cases without histology confirmation of the diagnosis may have had another type of brain tumor or even brain metastases. Such misclassifications inevitably bias the result towards unity. It is remarkable that 345 glioma cases were stratified according to grade I–IV, although histopathology was available only for 328 cases. In our studies on brain tumors we have histopathology verification of all of the diagnoses. Also, the total number of included cases [25] is not completely consistent with those reported to the Swedish Cancer Registry as we have discussed elsewhere [55]. The study included cases from neurosurgery, oncology and neurology clinics as well as regional cancer registries in the study areas.

Among the controls in the glioma and meningioma study 282 (29%) refused to participate [25]. Among some of these non-responders a short interview was made and only 34% reported regular use of a cellular telephone compared with 59% of the responders. If this discrepancy extends to the total group of non-responders the true percentage of mobile phone users in controls would be approximately 52%. Hence this figure would be lower than in glioma (58% exposed) and acoustic neuroma cases (60%). Only for meningioma with 43% exposed cases a lower percentage was reported, however, considering the sex ratio (women:men) for meningioma of about 2:1 a lower percentage of mobile phone users has to be expected due to the lower rate of users among women. It should be noted that a similar procedure in another Interphone study yielded similar results regarding mobile phone use among responders and non-responders [17].

It was discussed in a medical dissertation [56] that: ‘Our Swedish study, that includes a large number of long-term mobile phone users, does not support the few previously reported positive findings, and does not indicate any risk increases neither for short-term or long-term exposures.’ Considering the methodological shortcomings and that in contrast to the cited assertion of ‘a large number of long-term users’ the study subjects included only 25 glioma and 12 meningioma cases with long-term use, its conclusion seems to be going a long way beyond what can be scientifically defended.

It might be mentioned that this area of research seems to be controversial *per se* with unfounded statements [57], easily rebutted [58] and not supported by evolving scientific evidence [59]. Statements on no risk for brain tumors based on short-time use of mobile phones [60] might be considered in a larger context [61].

We included in our studies use of mobile or cordless phone ‘any time’ in the exposed group and made dose-response calculations based on number of hours of cumulative use. The unexposed group included also subjects with use of wireless phones with ≤1-year latency period. On the contrary, mobile phone use in the Interphone studies was defined as ‘regular use’ on average once per week during at least 6 months, less than that was regarded as unexposed including also all use within <1 year before diagnosis. This definition of ‘regular use’ seems to have been arbitrary chosen and might have created both observational and recall bias in the interpretation of such a definition.

Use of cordless phones was not assessed or not clearly presented in the Interphone studies, e.g. [25,28]. We found a consistent pattern of an association between cordless phones and glioma and acoustic neuroma [11,12]. It has been shown that the GSM phones have a median power in the same order of magnitude as cordless phones [62]. Moreover, cordless phones are usually used for longer calls than mobile phones [11,12]. Including subjects using cordless phones in the “unexposed” group in studies on this issue, as for example in the Interphone investigations, would thus underestimate the risk and bias OR against unity.

The case participation was good in our studies, 88% for cases with benign brain tumors, 90% for malignant brain tumor cases and 89% for the controls. On the contrary case participation varied from 37% to 93% and control participation from 42% to 75% in the Interphone studies. Obviously low participation rates for cases and controls might give selection bias and influence the results in the Interphone studies.

Methodological issues in the Interphone studies have been discussed elsewhere [14,15,18,55,63–65]. It was concluded that the actual use of mobile phones was underestimated in light users and overestimated in heavy users. Random recall bias could lead to large underestimation in the risk of brain tumors associated with mobile phone use. It was further suggested that selection bias in the Interphone study resulted in under selection of unexposed controls. Refusal to participate was related to less prevalent use of mobile phones, and this could result in a downward bias in estimates of the disease risk associated with mobile phone use. As discussed by Kundi [18] there was also interview lag time between cases and controls in the Interphone studies that might have been a source of bias due to the fast increase of mobile phone use during the study period. This could have resulted in underestimation of risk.

For salivary gland tumors the results were based on three case-control studies. In the 10 year latency period the meta-analysis gave an almost significantly increased risk for ipsilateral use of mobile phones, and a non-significantly decreased risk for contralateral use. These results were based on few cases. Regarding NHL and testicular cancer some subgroup analysis yielded increased risks, but these results were based on low numbers. Use of mobile phone increased the risk significantly for melanoma of the eye. The study on intratemporal facial nerve tumors is not informative since

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it was based on few cases and included acoustic neuroma patients in the control group. It is concluded that all studies were hampered by low numbers of long-term users and need to be replicated for firm evidence of an association between use of mobile phones and these tumor types.

In summary our review yielded a consistent pattern of an increased risk for acoustic neuroma and glioma after >10 years mobile phone latency. Our studies showed also an association with use of cordless phones, an issue that has not been studied at all in most investigations or only rudimentary in two studies. We conclude that current standard for exposure to microwaves during mobile phone use is not safe for long-term exposure and needs to be revised.

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Mobile phone base stations—Effects on wellbeing and health

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Abstract

Studying effects of mobile phone base station signals on health have been discouraged by authoritative bodies like WHO International EMF Project and COST 281. WHO recommended studies around base stations in 2003 but again stated in 2006 that studies on cancer in relation to base station exposure are of low priority. As a result only few investigations of effects of base station exposure on health and wellbeing exist. Cross-sectional investigations of subjective health as a function of distance or measured field strength, despite differences in methods and robustness of study design, found indications for an effect of exposure that is likely independent of concerns and attributions. Experimental studies applying short-term exposure to base station signals gave various results, but there is weak evidence that UMTS and to a lesser degree GSM signals reduce wellbeing in persons that report to be sensitive to such exposures. Two ecological studies of cancer in the vicinity of base stations report both a strong increase of incidence within a radius of 350 and 400 m respectively. Due to the limitations inherent in this design no firm conclusions can be drawn, but the results underline the urgent need for a comprehensive investigation of this issue. Animal and in vitro studies are inconclusive to date. An increased incidence of DMBA induced mammary tumors in rats at a SAR of 1.4 W/kg in one experiment could not be replicated in a second trial. Indications of oxidative stress after low-level in vivo exposure of rats could not be supported by in vitro studies of human fibroblasts and glioblastoma cells.

From available evidence it is impossible to delineate a threshold below which no effect occurs, however, given the fact that studies reporting low exposure were invariably negative it is suggested that power densities around 0.5–1 mW/m^2 must be exceeded in order to observe an effect. The meager data base must be extended in the coming years. The difficulties of investigating long-term effects of base station exposure have been exaggerated, considering that base station and handset exposure have almost nothing in common both needs to be studied independently. It cannot be accepted that studying base stations is postponed until there is firm evidence for mobile phones.
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1. Introduction

Modern mobile telecommunication is based on a cellular system. Each cell is covered by a base station that keeps track of the mobile phones within its range, connects them to the telephone network and handles carry-over to the next base station if a customer is leaving the coverage area. Early mobile telecommunication systems had very large cells with tens of kilometers radius and were predominantly located along highways due to offering service mainly for car-phones. With the introduction of digital mobile phone systems cell sizes got much smaller and base stations were erected in densely populated areas. The limited power of mobile phones made it necessary to reduce the distance to the customers. The cell size depends on (1) the radiation distance of the mobile phone; (2) the average number of connected calls; (3) the topographic characteristics of the covered area and the surrounding buildings, vegetation and other shielding objects; and (4) the type of antenna used. There are essentially three types of cells presently making up mobile telecommunication networks: (1) macro-cells in areas of average to low number of calls; (2) micro-cells in densely populated areas and areas with high telecommunication traffic density; (3) pico-cells within buildings, garages, etc. The types of antennas used, although hundreds of different models are operated, can be subdivided into: omni-directional antennas that radiate in all horizontal directions with the same power; sector antennas

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that radiate the main beam in one sector only but have varying aperture (usually 120° or 90°). These antennas can be mounted on masts (that sometimes are in the shape of trees for protection of landscape or are otherwise hidden), on the top of buildings, on pylons, and micro- and pico-cell antennas on various other places (walls of houses, shops, indoors, etc.). The width of the beam in vertical direction is typically 6°, but due to the presence of side lobes the actual pattern is more complicated.

Digital base stations of the second generation (GSM, TDMA) and third generation (UMTS, CDMA) have typically a nominal power for each channel of 10–20 W, micro- and pico-cells up to about 4 and 2 W, respectively. Due to the antenna gain the EIRP in the direction of the main beam is much greater (by a factor of $10^{g/10}$, where g is the antenna gain in dB, typically between 40 and 60). Most base stations of the second generation operate with two channels, one broadcast control channel (BCCH, channel used for transmitting information about the network, the location area code, frequencies of neighboring cells, etc.) and one traffic channel (TCH, channel used for transmission of calls), for third generation systems, due to code division multiplexing, control information needed for the maintenance of the system is at present transmitted together with the actual information (calls, pictures, etc.) within one broad-band channel. GSM systems operate the BCCH with all time slots occupied and therefore at maximal power, whereas TCH has as many time slots active as necessary to operate all active transmission not covered by the BCCH. Field strength at ground level depends on the characteristics of the antenna. Because the main beam reaches ground level typically in 50–200 m distance, in case of free sight to the antenna, maximum field strength is reached at that distance. However, due to the side lobes ups and downs of field strength occur as one approach the base station. In areas where objects are shadowing the beams, patterns are still more complex because of diffraction and reflection and multi-path propagation with constructive as well as destructive interference.

Free field propagation from the antenna along the main beam follows the law: $P(x) = \mathrm{EIRP}/(4\pi \cdot x^2)$, with $P(x)$ the power flux density in x meters distance and EIRP the equivalent isotropic radiated power of the antenna. Significant deviations from this expectation occur due to the side lobes, presence of interfering objects, differences in vertical beam width, and variations in the number of active transmissions. For these reasons distance to the antenna is a poor proxy for exposure level.

Since the early 1990s tens of thousands of base stations have been erected in countries where digital networks were introduced. While older systems with their low number of base stations have hardly received public attention, the vast increase in base stations has led to public concerns all over the world. Anecdotal reports about various effects on wellbeing and health have led also to an increased awareness of physicians [1,2] and increased research efforts have been demanded [3]. Despite these professional and public concerns, the WHO International EMF Project has discouraged research into effects of base stations, because it deemed research into effects of mobile phones of higher priority. This position was changed in 2003 when the new research agenda recommended studies around base stations. In 2006 it was again stated that research into potential health effects of base station is of low priority [4].

Due to these circumstances only very few investigations of effects of base stations on wellbeing and health exist. In addition some experimental studies have been conducted, most of which address the problem of short-term effects on complaints and performance.

The following review summarizes available evidence and critically assesses the investigations as to their ability to support or dismiss a potential effect of microwave exposure from base stations on wellbeing and health.

2. Epidemiological investigations

2.1. Wellbeing and performance

Santini et al. [5,6] report results of a survey in France to which 530 individuals (270 men and 260 women) responded. Study subjects were enrolled through information given by press, radio, and website, about the existence of a study on people living near mobile phone base stations. Frequency for each of 18 symptoms was assessed on a 4 level scale (never, sometimes, often, and very often). Participants estimated distance to the base station using the following categories: <10 m, 10–50 m, 50–100 m, 100–200 m, 200–300 m, >300 m. For comparison of prevalence of symptoms >300 m served as reference category. For all symptoms a higher frequency of the categories 'often' or 'very often' was found at closer (self-reported) distance to the base station. Fatigue, headaches, and sleeping problems showed highest relative increase. Due to a less than optimal statistical analysis comparing each distance category separately with the reference category the overall response pattern can only be assessed qualitatively. Fig. 1 shows relative prevalence averaged over all symptoms as a function of self-reported distance to the antenna. Interestingly the function is not monotonous but shows, after an initial drop, an increase at a distance of 50–100 m. Because of the fact that in many cases this is the distance at which the main beam reaches ground level this may indicate a relationship to actual exposure levels.

This study was a first attempt to investigate a potential relationship between exposure to base station signals and health and has, therefore, several shortcomings: (1) participants selected themselves into the study group by responding to public announcements; (2) distance was self-reported and no attempt was made to validate these reports (a German cross-sectional study in over 30,000 households revealed that more than 40% did not know they were living in the vicinity of a base station [7]); (3) no assessment of subjects' concerns about the base station; and (4) no measurement or calcula-

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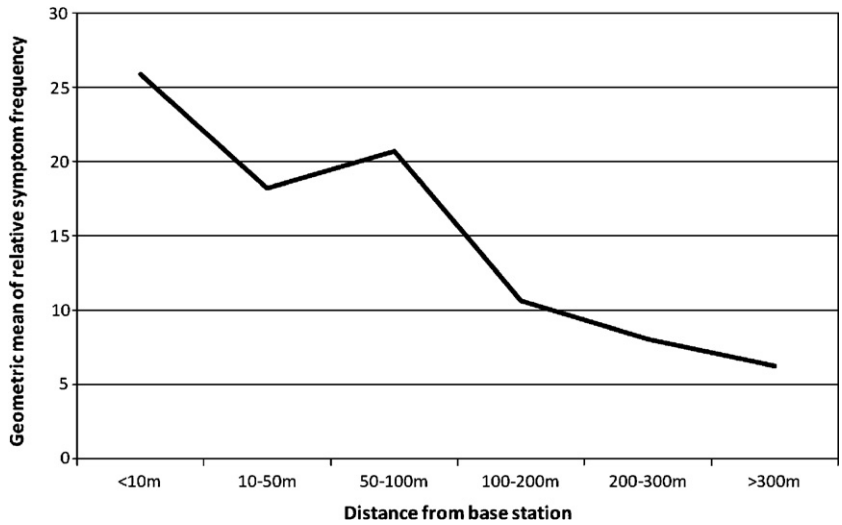

Fig. 1. Relative symptom frequency averaged over all 33 reported symptoms from Santini et al. [5] as a function of distance from base station.

tion of actual exposure. Although selection bias and wrong estimation of distance to the base station could have led to a spuriously increased prevalence of symptoms, the pattern of symptom frequency as a function of distance is intriguing and suggests that part of the increased symptom prevalence could be due to exposure because people do not know the typical pattern of field strengths found in the vicinity of base stations.

A Spanish version of the questionnaire as applied in the French study was distributed in La Nora, a small town in Murcia, Spain, to about 145 inhabitants [8]. Overall 101 questionnaires (from 47 men and 54 women) were included in the analyses. Electric field strength in the frequency range 1 MHz to 3 GHz was measured in the bedrooms of the participants. Data were analyzed in two different ways: first subjects were subdivided into those living less than 150 m from the base station and a second group living more than 250 m away (according to self-reports); the average exposure level of the first group was 1.1 mW/m^2, and of the second group 0.1 mW/m^2; self-reported symptom severity was compared across these groups. The second method correlated log transformed field strengths with symptom scores. The majority of symptoms showed a relationship both by comparison of the contrast groups according to distance from the base station as well as when correlated to measured field strength. Strongest effects were observed for headaches, sleep disturbances, concentration difficulties, and discomfort.

In contrast to the French investigation the study has assessed actual exposure by short-term measurements in the bedrooms of participants. The fact that both, reported distance as well as measured field strength, correlated with symptom severity supports the hypothesis of an association between microwaves from the base station and wellbeing. However, because subjects knew that the intention of the study was to assess the impact of the base station there is a potential for bias. Also concerns of the participants about effects of the base station on health were not assessed. Furthermore, method of selection of participants was not reported.

In a cross-sectional study in the vicinity of 10 GSM base stations in rural and urban areas of Austria, Hutter et al. [9] selected 36 households randomly at each location based on the characteristics of the antennas. Selection was done in such a way as to guarantee a high exposure gradient. Base stations were selected out of more than 20 locations based on the following criteria: (1) at least 2 years operation of the antenna; (2) no protest against it before or after erection; (3) no nearby other base station; (4) transmission only in the 900 MHz frequency band. (The last two criteria were not fully met in the urban area.) In order to minimize intervention of interviewers all tests and questionnaires were presented on a laptop computer and subjects fulfilled all tasks on their own. Wellbeing was assessed by a symptoms list (v. Zerssen scale), sleeping problems by the Pittsburgh sleeping scale. In addition several tests of cognitive performance were applied. Concerns about environmental factors were inquired and sources of EMF exposure in the household were assessed as well. It was not disclosed to the subjects that the study was about the base station, but about environmental factors in general. Among other measurements high-frequency fields were assessed in the bedrooms. From the measured field strength of the BCCH maximum and minimum exposure to the base station signals were computed. In addition overall power density of all high-frequency fields was measured. Results of measurements from 336 households were available for analysis. Exposure from the base station was categorized into three ranges: below 0.1 mW/m^2, between 0.1 and 0.5 mW/m^2, and above 0.5 mW/m^2. Cognitive performance tended to be better at higher exposure levels and was statistically significant for perceptual speed after correction for confounders (age, gender, mobile phone use, and concerns about the base station). Subjective symptoms were generally more frequent at higher exposure levels and statistically increased prevalence was found for headaches, cold hands or feet, and concentration difficulties. Although participants reported more sleeping problems at higher exposure

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levels, this effect was removed after controlling for concerns about the base station.

Despite limitations inherent in the cross-sectional study design the methodological problems mentioned in the French and Spanish investigations were avoided. Authors conclude: "The results of this study indicate that effects of very low but long lasting exposures to emissions from mobile telephone base stations on wellbeing and health cannot be ruled out. Whether the observed association with subjective symptoms after prolonged exposure leads to manifest illness remains to be studied."

A study in employees working within or opposite a building with GSM base station antennas on the roof was reported by Abdel-Rassoul et al. [10]. The investigation took place in Shebin El-Kom City, Menoufiya Governorate, Egypt, where the first mobile phone base station was erected in 1998 on a building for agricultural professions. Overall 37 subjects working within this building and 48 subjects working in the agricultural directorate about 10 m opposite the building were considered exposed. A control group, working in another building of the agricultural administration located approximately 2 km away, consisted of 80 persons. Participants completed a structured questionnaire assessing educational and medical history. A neurological examination was performed and a neurobehavioral test battery (tests for visuomotor speed, problem solving, attention and memory) was presented. The combined exposed groups were compared to the control group that was matched by sex, age and other possible confounders. Statistical analysis accounted for these variables. Further comparisons were performed between subjects working in the building with the base station on the roof and those opposite. Exposed subjects performed significantly better in two tests of visuomotor speed and one test of attention, in two other tests the opposite was the case. The prevalence of headaches, memory problems, dizziness, tremors, depressive symptoms, and sleep disturbances was significantly higher among exposed inhabitants than controls. Measurements conducted 3 years before the investigation revealed compliance with the Egyptian standard (80 mW/m^2) with values between 27 and 67 mW/m^2, but locations of the measurements were not specified.

Like in the study of Hutter et al. [9] it was not disclosed to the participants that the study was about the base station. An important aspect is studying employees that occupy the area of exposure for 8–16 h a day. Several possible confounders (age, sex, education, smoking, and mobile phone use) were considered and did not change the reported results. Other factors like stressful working conditions, indoor pollutants and other attributes of the work place were not assessed and might have had an effect on the reported symptoms. Although no recent measurements were available it can be assumed that both, subjects working within the building as well as those opposite the building with the base station are exposed at comparatively high levels. The picture of one antenna shown in the article indicates that the panel is slightly uptilted. It can be assumed that the sidelobes of the antenna are directed downwards into the building below the base station as well as into the opposite building. Measurements in Germany revealed that, in contrast to a general belief that there is no significant exposure in buildings below a base station antenna, the field strength in buildings below an antenna is almost equal to field strength in opposite buildings.

An experimental field trial was conducted in Bavaria [11] during three months before an UMTS antenna on a governmental building started operation. Based on a random sequence the antenna was turned on or off one, two, or three days in a row during 70 working days in winter 2003. Conditions were double-blind since neither the experimenters nor the participants knew whether the antenna was on or off. This was guaranteed by software manipulation of the antenna output that prohibited UMTS mobile phones from contacting the base station and by locating the computer controlling the antenna in a sealed room. The UMTS antenna operated at a mean frequency of 2167.1 MHz. The protocol has not been specified, but considering that no real transmission occurred it is assumed that only the service channel was used. The antenna had a down-tilt of 8° expected to result in rather high exposure within the building. Measured electric field strength in the rooms of the participants varied between the detection limit of the field probe (0.05 V/m) and 0.53 V/m (corresponding to 0.75 mW/m^2) with an average of 0.10 ± 0.09 V/m (corresponding to 0.03 mW/m^2). Participants should answer an online questionnaire on each working day they were in the office in the morning when they arrived and in the evening shortly before leaving. The questionnaire consisted of a symptom list with 21 items, and in the evening participants should state whether or not they considered the antenna has been on during this day and whether they considered, if they experienced any adverse effects, these effects due to the base station. From approximately 300 employees working in the building 95 (28 females, 67 males) that answered the questionnaire on at least 25% of the working days were included in the analysis.

None of the 21 symptoms showed a statistically significant difference between days on and days off. A more comprehensive analysis of the overall score across all 21 items applying a mixed model with subjects as random factor and autoregressive residuals revealed a tendency ($p = 0.08$) for an effect of actual exposure on the difference between morning and evening values. Self-rated electrosensitivity had a significant effect on evening scores but did not affect difference scores. As expected, subjective rating of exposure had a significant influence both, on evening scores and score difference. Correct detection rate of base station transmission mode was 50% and thus equal to chance. No person was able to detect operation mode correctly on significantly more days than expected.

The study design was a great strength of this pilot investigation. It combined the advantages of a field trial with the rigorous control of exposure conditions in an experiment. However, there are a number of severe shortcomings too: first, no correction for actual exposure has been applied. As

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stated above, exposure varied considerably within the building and some participants were not exposed at detectable levels at all. The resulting exposure misclassification leads to a bias towards the null hypothesis. Furthermore, it was not specified which UMTS protocol was actually transmitted. Another important limitation is the quite low exposure even in the offices with the highest levels. Problems with the statistical evaluation are indicated by a highly significant time factor suggesting insufficient removal of autocorrelation. Finally, the symptom list contains several items that were not implicated previously as related to exposure from base stations (e.g. back pain). Such items reduce the overall power to detect an effect of base station exposure.

A cross-sectional study based on personal dosimetry was conducted in Bavaria [12]. In a sample of 329 adults (173 females, 155 males, and 1 unknown) chronic and acute symptoms were assessed. Chronic symptoms were taken from the Freiburger Beschwerdeliste and acute symptoms from the v. Zerssen list. Symptoms assessed were headache, neurological symptoms, cardiovascular symptoms, concentration problems, sleeping disorders and fatigue. Participants wore a dosimeter (Maschek ESM 140) for 24 h on the upper arm on the side used for holding a phone (during the night the dosimeter was placed next to the bed). The dosimeter measured exposure in frequency bands including GSM 900 up- and down-link, GSM 1800 up- and down-link, UMTS, DECT and WLAN (2.45 GHz).

Acute symptoms at noon and in the evening were dichotomized and related to exposure during the previous 6 h (night time measurements were considered biased and not analyzed). Exposure was expressed in percent of the ICNIRP reference levels. Odds ratios for the different symptom groups were computed in relation to exposure subdivided into quartiles with the first quartile as reference. Similarly, dichotomized chronic symptoms were related to average day time exposure levels. None of the symptom groups was significantly related to exposure. Odds ratios for headaches and cardiovascular symptoms during the last 6 months were increased for all three tested exposure quartiles (for headaches odds ratios were: 1.7, 2.7, and 1.2 for 2nd to 4th quartile; for cardiovascular symptoms these figures were 1.4, 3.3, and 2.4). But none of these odds ratios was statistically significant. Acute symptoms at noon and in the evening showed a tendency for lower prevalence of fatigue at higher exposure levels. Odds ratios for headaches and concentration problems in the evening were increased at higher exposure levels in the afternoon but also these results were statistically not significant (odds ratios for headaches were 1.7, 1.6, 3.1 and for concentration problems 1.4, 2.0, 1.4 for 2nd to 4th quartile of afternoon exposure levels).

Exposure was low and ranged from a daytime average of 0.05 V/m (at or below the limit of determination) to 0.3 V/m (corresponding to 0.24 mW/m^2 power density). (In order to make results comparable to other investigations figures expressed in percent of ICNIRP reference levels were recalculated to field strengths and power densities). Quartiles for daytime exposure were: up to 0.075 V/m, 0.075 to 0.087 V/m, 0.087 to 0.110 V/m, and 0.110 to 0.3 V/m. It can be seen that the first three quartiles are almost indiscernible with a ratio of the upper limit of the third and first quartiles of only 1.5.

Although the study of Thomas et al. [12] was the first one using personal dosimetry in the context of investigating effects of exposure to mobile phone base station signals on wellbeing it has not explored the potential of an almost continuous exposure measurement. Only average exposure was computed and the probably most important nighttime values were left out. A number of different exposure metrics should have been assessed, like duration of exposure above a certain limit, maximum exposure level, longest period below limit of determination, and variability of exposure levels to name but a few. Furthermore, prevalence of symptoms was so low that the power of the investigation to detect even substantially increased risks was inferior (less than 25%). Despite these shortcomings the study has its merits as a first step in using personal dosimetry. An earlier report of the group [13] with a comparison between two personal dosimeters (Maschek and Antennessa) demonstrated that improvements are necessary before personal dosimetry can be successfully used in epidemiological studies.

A large population-based cross-sectional study was conducted in the context of the German 'Mobile Phone Research Program' in two phases [7]. In the initial phase 30,047 persons from a total of 51,444 (58% response rate) who took part in a nationwide survey also answered questions about mobile phone base stations. Additionally a list of 38 health complaints (Frick's list) was answered. Distance to the nearest base station was calculated based on geo-coded data of residences and base stations. In the second phase, all respondents (4150 persons) residing in eight preselected urban areas were contacted. In total, 3526 persons responded to a postal questionnaire (85% response rate) including questions about health concerns and attribution of symptoms to exposures from the base station as well as a number of standardized questionnaires: the Pittsburgh Sleep Quality Index, the Headache Impact Test, the v. Zerssen list of subjective symptoms, the profile of mental and physical health (SF 36), and a short version of the Trier Inventory of Chronic Stress. Overall 1808 (51%) of those that responded to the questionnaire agreed to have EMF measurement taken in their homes. Results of the large survey from the first phase of the study revealed a fraction of 10% of the population who attributed adverse health effects to the base station. An additional 19% were generally concerned about adverse effects of mobile phone base stations. Regression analysis of the symptoms summary score on distance to the base station (less or more than 500 m) and attribution/concerns about adverse effects adjusted for possible confounders (age, gender, SES, region and size of community) revealed a small but significant increase of the symptom score at closer distance to the base station. Higher effects, however, were obtained for concerns about adverse effects of the base station (with higher scores for those concerned) and still higher effects for

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those that attributed their health problems to exposures from mobile phone base stations. The latter result is only to be expected because attribution presupposes existence of symptoms and hence those with attribution must have higher scores than those without. Because effects of concerns/attribution were accounted for in the multivariate model, effect of distance to the base station is independent of these concerns or attributions. In the second phase measurements in the bedrooms revealed an overall quite low exposure to EMFs from the base station. Only in 34% of the households was the exposure above the sensitivity limit of the dosimeters of 0.05 V/m (~7 μW/m^2). On average power density was 31 μW/m^2 and the 99th percentile amounted to 307 μW/m^2. A dichotomization at the 90th percentile (exposure above 0.1 V/m, corresponding to 26.5 μW/m^2) did not indicate any effect of exposure on the different outcome variables but effects of attribution on sleep quality and overall symptom score (v. Zerssen list).

This large study has a number of important advantages: it started from a representative sample of the German population with over 30,000 participants and the second phase with a regional subsample had a participation rate of 85%. Furthermore, several well-selected standardized tests were used in the second phase. Results of the first phase are essentially in line with the Austrian study of Hutter et al. [9]. Not only the fraction with attribution of health complaints to exposure from the base station (10%) is identical, but also the higher symptom score in proximity to the base station independent of concerns/attributions found in the previous study has been replicated. However, the study has also severe shortcomings, most notably: the failure to include a sufficient number of participants that can be considered as exposed to microwaves from the base station. Note that Hutter et al. [9] selected households based on the characteristics of the antennas in such a way as to guarantee a large exposure gradient. In the randomly selected households of the study by Blettner et al. [7] the 90th percentile used as cutoff was well below the median (~100 μW/m^2) of the earlier investigation and the 99th percentile was still below the level (500 μW/m^2) that was found to increase the prevalence of several symptoms. Therefore it is unlikely that the investigation of the second phase could detect an effect if it occurs at levels consistent with those reported by Hutter et al. [9].

2.2. Cancer

Despite considerable public concerns that exposure to microwaves from mobile phone base stations could be detrimental to health and may, in particular, cause cancer, up to now only two studies of cancer in the vicinity of base stations applying basically an ecological design have been published.

In a Bavarian town, Neila, the physicians of the town conducted an epidemiological investigation [14] to assess a possible association between exposure to base station radiation and cancer incidence. The design used was an improved ecological one. Two study areas were defined: one within a circle of 400 m radius around the only base stations (two that were located in close proximity to each other) of the town, and one area further than 400 m from the base stations. Within these defined areas streets were randomly selected (after exclusion of a street where a home for retired people was situated) and all general practitioners of the town that were active during the whole period of operation of the base stations (one base station started operation September 1993 the other December 1997) scanned their files for patients living in the selected streets. Overall 967 individuals were found, constituting approximately 90% of the reference population. The study period 1/1994 to 3/2004 was subdivided into two segments: The first 5 years of operation of the base station (1994 through 1998) and the period from the sixth year, 1999, until 3/2004. Among the identified individuals 34 incident cases of cancer (excluding non-melanoma skin cancer) were found. Assessment of cancer cases was assumed to be complete and all cases were verified histologically and by hospital discharge letters (note that there is no cancer registry in Bavaria). Age distribution was similar in the two areas with a mean age of 40.2 years in both, the area within 400 m of the base station and the area further apart. Crude annual cancer incidence in the first 5 years after start of operation of the base station was 31.3×10^{-4} and 24.7×10^{-4} in the closer and farther area, respectively. In the second period these figures were 76.7×10^{-4} and 24.7×10^{-4}. The age and gender adjusted expected value of incident cancer cases in the study population based on data from Saarland, a German county with a cancer registry, is 49×10^{-4}. In the second period cancer incidence in the area within 400 m of the base station was significantly elevated, both, compared to the area further away as well as compared to the expected background incidence. The incidence in the region further apart was reduced but not significantly when compared to the expected value.

Although this so-called Neila-study applied an improved ecological design with a random selection of streets and inclusion of some information from selected individuals, it is still subject to potential bias because relevant individual risk factors could not be included in the analyses.

A similar though less rigorous study has been performed in Netanya, Israel. Wolf and Wolf [15] selected an area 350 m around a base station that came into operation 7/1996. The population within this area belongs to the outpatient clinic of one of the authors. The cohort within this area consisted of 622 people living in this area for at least 3 years at study onset, which was one year after start of operation of the base station and lasted for 1 year. Overall cancer incidence within the study area was compared to a nearby region, to the whole city of Netanya, and to national rates. In the second year after onset of operation 8 cancer cases were diagnosed in the study area. In the nearby area with a cohort size of 1222 individuals, 2 cases were observed. Comparison to the total population with an expected incidence of 31×10^{-4} indicates a pronounced increase in the study area with an incidence of 129×10^{-4}. Also against the whole town of Netanya an increased incidence was noted especially in women. In an

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addendum authors noted that also in the subsequent year 8 new cases were detected in the study area while in the period 5 years before the erection of the base station 2 cases occurred annually. Spot measurements of high frequency fields were conducted in the homes of cancer cases and values between 3 and 5 mW/m^2 were obtained. Although these values are well below guideline levels, they are quite high compared to typical values measured in randomly selected homes [7].

Also in the case of the Netanya study lack of information on individual risk factors makes interpretation difficult. Furthermore, migration bias has not been assessed although only subjects were included that occupied the area for at least 3 years. The short latency after start of operation of the base station rules out an influence of exposure on induction period of the diseases. The substantial increase of incidence is also hardly explainable by a promotional effect.

3. Experimental studies

3.1. Experiments in human sensitive and non-sensitive individuals

There are persons who claim to suffer from immediate acute as well as chronic effects on exposure to EMF and in particular to those from mobile phones or their base stations. Often these persons are called EMF hypersensitive (EHS). The preferred term agreed upon at a WHO workshop [16] was Idiopathic Environmental Intolerance with attribution to EMF (IEI-EMF). Indeed, it would be a misunderstanding to confuse EHS with allergic reactions; rather these persons react with different unspecific symptoms such as headaches, dizziness, loss of energy, etc. Whether these persons have actually the ability to tell the difference between situations with and without exposure to EMFs is an open question. In a recent review Röösli [17] concluded that "...the large majority of individuals who claim to be able to detect low level RF-EMF are not able to do so under double-blind conditions. If such individuals exist, they represent a small minority and have not been identified yet." However, it is important to differentiate between EMF sensitivity and sensibility [18]. Independent of the question whether or not there are individuals that sense the presence of low levels of EMFs such as those measured in homes near mobile phone base stations, there could well be an effect of such exposures on wellbeing and performance even under short-term exposure conditions. In several experimental investigations this question has been addressed by exposure of persons with self-reported symptoms and also in persons without known adverse reaction to an assumed exposure.

The first of these investigations was carried out by the Netherlands Organization for Applied Scientific Research (TNO) and published as a research report [19]. Two groups of persons were included in the experiment. One group consisted of individuals (25 females, 11 males) who have previously reported complaints and attributed them to GSM exposure. The other group consisted of subjects without such complaints (14 females, 22 males). Four experimental conditions were applied in a double-blind fashion: Sham exposure, exposure to 945 MHz GSM, 1840 MHz GSM, and 2140 MHz UMTS. Each participant underwent sham exposure and two of the active exposure conditions. Sequence of exposure was balanced such that each active exposure condition was tested equally often at each of three experimental sessions. Each experimental session and a training session lasted for 45 min. All three experimental sessions and the training session were completed on one day for each participant. Both, for GSM and UMTS exposure, a base station antenna was used and a simulated base station signal was transmitted during sessions. For the GSM conditions a 50% duty cycle (4 slots occupied) was applied with pulses of peak amplitudes of 1 V/m (0.71 V/m effective field strength; corresponding to 1.3 mW/m^2). For UMTS exposure a protocol was used with different low frequency components and an effective field strength of 1 V/m (corresponding to 2.7 mW/m^2). During each session several performance tests were conducted and immediately after each session a wellbeing questionnaire was administered (an adapted version of the Quality-of-Life Questionnaire of Bulpitt and Fletcher [20] with 23 items).

Overall score of wellbeing was significantly reduced in both groups after the UMTS condition compared to sham exposure. Considering subscores anxiety symptoms, somatic symptoms, inadequacy symptoms, and hostility symptoms were increased in the groups of sensitive individuals whereas in the control group only inadequacy symptoms were increased after UMTS exposure compared to sham. No effects were found in the two GSM exposure conditions. Concerning cognitive performance both groups revealed significant exposure effects in almost all tests in different exposure conditions. In most of these tests reaction time was reduced except for one simple reaction time task.

This study had an enormous echo both in the media as well as in the scientific community because it was the first experimental investigation with very low exposure to base station like signals and in particular to UMTS signals, and because it was conducted by a highly respected research institution reporting systematic effects of exposure that seemed to support citizens initiatives claiming that base stations have adverse effects on wellbeing and health. Immediately doubts were expressed that results could be biased due to a faulty methodology. In fact, study design can be improved. First of all testing all exposure conditions on the same day has the advantage to reduce variance from between day differences but could cause transfer effects if biological reactions do not immediately terminate after end of exposure and start of the next condition. Also time-of-day effect from chronobiological variations could be superimposing the reactions from exposure. Such effects are sometimes not removed by balancing exposure conditions. Second, not all subjects were tested under all exposure conditions. The decision to reduce total experimental duration by presenting only two of the three exposure conditions together with sham was sound but

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on the other hand led to a reduced power. Several other arguments such as the different gender distribution in the two groups are not very important because each subject served as his/her own control and comparison between groups was not important in this investigation. Other criticism was expressed against statistical analysis. No correction for multiple testing was applied. While some advice protection against inflation of type I error others recommend correction only for crucial experiments and not for pilot studies like this. Another, more serious, criticism was put forward against disregarding sequence of experimental conditions. As mentioned above, sequence, transfer, and time-of-day effects could have compromised results because such effects are not completely removed by balancing exposure sequence. Due to this criticism several studies were planned that should investigate whether the effects observed in the TNO study are robust and could be replicated under improved study designs.

One of these experiments was performed in Switzerland [21]. Like in the TNO study, two groups of individuals were included: one with self-reported sensitivity to RF-EMF (radio-frequency EMF) and a reference group without complaints. The first group consisted of 33 persons (19 females, 14 males) and the reference group of 84 persons (43 females, 41 males). The experiment consisted of three experimental and one training session each 1 week apart performed on the same time of day (±2 h). Design was a randomized double-blind cross-over design like in the case of the TNO study, however, with a week between sessions and with all subjects tested under all experimental conditions that were solely simulated UMTS base station exposure at 1 V/m, 10 V/m and sham. The same UMTS protocol as in the TNO study was used. Each exposure condition lasted for 45 min. During exposure two series of cognitive tasks were performed. After each exposure condition the same questionnaire as has been used in the TNO study was applied and questions about sleep in the previous night, alcohol, coffee consumption, etc., were asked. Moreover, subjects had to rate the perceived field strength of the previous exposure condition on a visual analogue scale. In addition, before and after each session the short Questionnaire on Current Disposition [22] was answered by participants. Questionnaires were presented in a separate office room.

Except for a significant reduction of performance speed of sensitive participants in the 1 V/m condition in one of six cognitive tests no effect of exposure was detected. In particular, no reduction of wellbeing neither as assessed by the TNO questionnaire nor from scores of the Questionnaire on Current Disposition was found. Also correlation between perceived and real exposure was not more often positive than expected from chance. Fig. 2 compares results of the TNO study and the results of Regel et al. [21] for the matching conditions (UMTS at 1 V/m). There are some notable differences between the two studies: first, the reference group in the study of Regel et al. [21] had significantly higher scores (reduced wellbeing) as the reference group in the TNO study in both the sham and the UMTS 1 V/m condition; second,

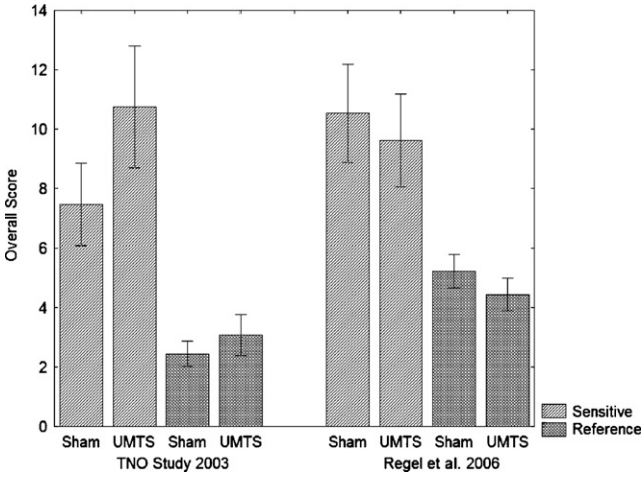

Fig. 2. Comparison of mean (±SEM) overall wellbeing scores (TNO questionnaire) obtained in the TNO study [19] and in the study of Regel et al. [21] for the matching conditions: Sham exposure and UMTS exposure at 1 V/m in sensitive participants and the reference group.

average scores from sensitive participants after exposure at 1 V/m are comparable in both studies but the sham condition resulted in much lower scores (better wellbeing) in the TNO study. There are several explanations for this difference between the two studies. It is possible that the reference group in the TNO study consisted of exceptionally robust individuals. The fraction of males was higher in the TNO study and males have typically lower scores. However, considering that the reference group in the TNO study was almost 10 years older (mean age 47 years) as compared to the study of Regel et al. [21] (mean age 38 years) this is not a satisfactory explanation. It is possible that the basic adversity of the experimental setup was higher in the latter study resulting in overall greater reduction of wellbeing. That this has not been observed in the sensitive group assumed to be more vulnerable to a 'nocebo' effect (the nocebo effect is the inverse of the placebo effect describing a situation when symptoms occur due to expecting adverse reactions) in both conditions could be due to a ceiling phenomenon. Although the study by Regel et al. [21] had an improved design and could not replicate the earlier findings of the TNO study, doubts exist whether this can be considered a refutation of an effect of UMTS exposure on wellbeing.

Another experimental study in sensitive and non-sensitive participants has been conducted in Essex, Great Britain, by Eltiti et al. [23]. The experiment consisted of two phases: an open provocation test and a series of double-blind tests. In the open provocation phase 56 self-reported sensitive and 120 non-sensitive control individuals participated. Of these, 44 sensitive (19 females, 25 males) and 115 controls (49 females, 66 males) also completed the double-blind tests. Participants took part in four separate sessions each at least 1 week apart. First session was the open provocation trial, sessions 2–4 were double-blind exposure trials with a sham, a GSM and a UMTS exposure condition. Double-blind sessions were reported to last for 1.5 h, however, Table 1 of the

article showed an overall length of 48 min only. GSM exposure was a simulated base station signal with both a 900 and a 1800 MHz component each at an average level of 5 mW/m^2 and with a simulated BCCH with all time slots occupied and a TCH with a simulated 40% call activity resulting in a total of 10 mW/m^2 GSM exposure at the position of the participants (corresponding to 1.9 V/m E-field strength). The UMTS signal had a frequency of 2020 MHz with a power flux density of 10 mW/m^2 over the area where the participant was seated. Traffic modeling for the UMTS signal was achieved using a test model representing a realistic traffic scenario, with high peak to average power changes. During double-blind sessions participants watched a BBC "Blue Planet" video for 20 min, performed a mental arithmetic task for 20 min, performed a series of cognitive tasks lasting 8 min, and made 'on/off' judgments. During the first 40 min every 5 min subjective wellbeing was recorded on visual analogue scales (VAS) measuring anxiety, tension, arousal, relaxation, discomfort, and fatigue. In addition a symptom scale consisting of 57 items was answered. During the whole period physiological measurements of heart rate, blood volume pulse, and skin conductance were performed.

Physiological measurements revealed higher average values for sensitive individuals compared to controls which were especially high under UMTS exposure conditions. Symptom list did not reveal any differences between double-blind conditions, but the overall frequency of solicited symptoms was low. Concerning subjective wellbeing as assessed by VAS there were increased values for anxiety, tension, and arousal under GSM and especially UMTS exposure conditions. Combining all scores of the six scales (with relaxation reflected) reveals a significant increase during UMTS exposure compared to sham for the sensitive group and a significant reduction for the control group (see Fig. 3). Judgment of participants about presence of exposure was not correct more often than inferred from chance.

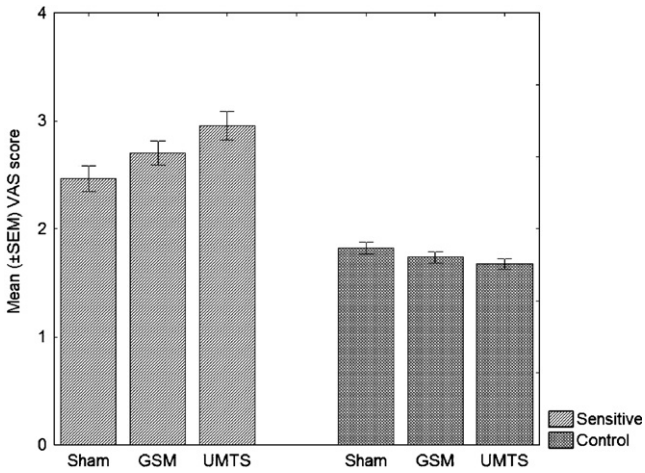

Fig. 3. Mean (±SEM) total visual analogue scale scores computed from Table 2 of Eltiti et al. [23] during sham, GSM, or UMTS exposure in sensitive and control individuals.

The increased values for anxiety, tension, and arousal found in this investigation were interpreted by the authors as due to an imbalance in the sequence of conditions with UMTS being more often the first exposure condition presented in the double-blind sessions. The imbalance was due to not reaching the predefined sample size. This points to the importance of setting the block size for randomization to a low level (e.g. in this experiment with 6 possible exposure sequences a block size of 18 would have been appropriate). Interpretation of authors, however, is questionable as pointed out by Röösli and Huss [24]. For arousal tabulated values stratified for sequence of presentation (Table 3 in [23]) demonstrates that the difference between sham and UMTS is present regardless of sequence of presentation. An additional analysis of the authors presented in response to the criticism in their statistical analysis seems to support their view that the observed difference to sham is due to a sequence effect. However, it seems that this analysis has not been correctly applied as the sequence was introduced as a between subjects factor which corrects only the interaction between group and condition. Also the figure they provided [23] is inconclusive as it only demonstrates what is already known: that first exposure leads to higher reduction of wellbeing (higher values of arousal). This investigation, although well designed and applying a more realistic exposure scenario than the other two studies, leaves some questions open. Despite an apparent corroboration of the findings of the TNO study, the imbalance in the sequence of exposures makes it difficult to decide whether the interpretation of authors that the observed effect is due to an excess number of UMTS exposures presented first in the sequence is correct or an actual effect occurred. Irrespective of these difficulties, consistent with the other investigations, wellbeing was not strongly affected.

There are several other investigations of a similar type that have been completed and already reported at scientific meetings (e.g. Watanabe, Japan; Augner, Austria, personal communication) but have not yet been published.

3.2. Animal and in vitro experiments

Anane et al. [25] applied the DMBA (7,12-dimethylbenz(a)anthracene) model of mammary tumor induction in female Sprague–Dawley rats to test whether a sub-chronic exposure to microwaves from a GSM-900 base station antenna affects tumor promotion or progression. Exposure was 2 h/day, 5 days/week for 9 weeks starting 10 days after application of 10 mg DMBA administered at an age of animals of 55 days. Exposure was applied in an anechoic chamber with animals placed in Plexiglas compartments that confined animals to a position parallel to the E-field. Details of the exposure protocol were not provided. Two series of experiments were conducted with four groups of 16 animals each. In the first experiment groups were: sham, 1.4, 2.2, and 3.5 W/kg whole-body SAR, and the second experiment with sham, 0.1, 0.7, and 1.4 W/kg. In the first experiment the tumor incidence rate was significantly increased at 1.4

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and 2.2 W/kg exposure, while in the second experiment the incidence at 1.4 W/kg was significantly reduced.

The experiment by Anane et al. [25] is inconclusive not only because of the divergent results of the two experiments at the same exposure condition (1.4 W/kg SAR) but mainly because of the insufficient size of experimental groups. With a 70% background tumor incidence as observed in this investigation even for an increase to 100% in the exposed group the power to detect this difference at a significance level of 5% is less than 60%. Furthermore, considering experimental and biological variation substantial differences may occur by chance simply due to different distribution of background risk between experimental groups. Therefore, in contrast to the statement of authors that relevant differences would be detected with 16 animals per group, the study was severely underpowered and prone to spurious effects from uneven distribution of background risk. Also stress from confinement of animals could have contributed to the ambiguous results.

Yurekli et al. [26] report an experiment in male Wistar albino rats with the aim to analyze oxidative stress from whole-body exposure to a GSM 945 MHz signal at a SAR level of 11.3 mW/kg. In a gigahertz transverse (GTEM) cell a base station exposure in the far field was simulated. Two groups of rats, 9 animals in each group, were either exposed 7 h a day for 8 days or sham exposed. At the end of the exposure blood was withdrawn and malondialdehyde (MDA), reduced glutathione (GSH), and superoxide dismutase (SOD) were measured. MDA as well as SOD was significantly increased after exposure compared to sham, while GSH was significantly reduced. These results indicate that exposure may enhance lipid peroxidation and reduce the concentration of GSH which would increase oxidative stress. A disadvantage in this experiment was that the experiments were carried out sequentially and therefore animals differed in weight and no blinding could be applied.

In a series of experiments conducted in the Kashima Laboratory, Kamisu, Japan, different in vitro assays were applied to test whether irradiation with 2.1425 GHz, which corresponds to the middle frequency allocated to the down-link signal of IMT-2000 (International Mobile Telecommunication 2000, a 3G wide-band CDMA system), leads to cellular responses relevant for human health [27–29]. In the first experiment phosphorylation and gene expression of p53 was assessed [27]. In the second experiment heat-shock protein expression was evaluated in the human glioblastoma cell line A172 and human IMR-90 fibroblasts [28]. The effect of exposure of BALB/T3T cells on malignant transformation, on promotion in MCA (3-methylcholanthrene) treated cells, and on co-promotion in cells pretreated with MCA and co-exposed to TPA (12-O-tetradecanoylphorbol-13-acetate) was investigated by Hirose et al. [29]. In none of these experiments applying the same exposure regimen but different intensities and exposure durations (80 mW/kg SAR up to 800 mW/kg SAR, 2 h to several weeks) an effect of exposure was observed. Exposure facility comprised of two anechoic chambers allowing blinded simultaneous exposure of an array of 7 × 7 dishes in each chamber. Dishes were placed in a culture cabinet located in the anechoic chamber and exposed to radiation from a horn antenna whose signals were focused by a dielectric lens to obtain homogenous irradiation of the dishes. Details of the exposure protocol were not disclosed. It is stated that an IMT-2000 signal at a chiprate (a chip is a byte of information) of 3.84 Mcps was used for exposure. Assuming that it did not contain any low-frequency components as typically present in actual exposures the implications of the findings are unclear. It is rarely supposed that the high-frequency components of RF-EMFs itself are able to elicit any relevant effects in the 'low-dose' range. Rather low-frequency modulation may contribute to biological responses. Therefore, results of these Japanese investigations are of limited value for risk assessment, conditional on them having no such biologically relevant exposure attributes.

4. Discussion

Although there is considerable public concern about adverse health effects from long-term exposure to microwaves from mobile phone base stations there are only few studies addressing this issue. Several reasons can be identified for the scarcity of scientific investigations. First of all, WHO has discouraged studies of base stations, at least concerning cancer as endpoint, because retrospective assessment of exposure was considered difficult. Also COST 281 did not recommend studies of base stations and stated in 2002: "If there is a health risk from mobile telecommunication systems it should first be seen in epidemiological studies of handset use."

It is not appreciated that there are substantial and important differences between exposure to handsets and base stations. The typically very low exposure to microwaves from base stations, rarely exceeding 1 mW/m^2, was deemed very unlikely to produce any adverse effect. Assuming energy equivalence of effects a 24 h exposure at 1 mW/m^2 from a base station would be roughly equivalent to 30 min exposure to a mobile phone operating at a power of 20 mW (average output power in areas of good coverage). Because we do not know whether time-dose reciprocity holds for RF-EMF and whether there is a threshold for biological effects, there is no a priori argument why such low exposures as measured in homes near base stations could not be of significance for wellbeing and health. As an example from a different field of environmental health consider noise exposure: it is well known that at noise levels exceeding 85 dB(A) a temporary shift of hearing threshold occurs and that, besides this short-term effect, after years of exposure noise induced hearing loss may occur. On the other hand, at a sound pressure of more than a factor of 1000 below, when exposure occurs during the night, exposed individuals will experience sleep disturbances that could affect health in the long run. From this example it follows that exposure may have qualitatively different effects at different exposure levels.

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The most important difference between mobile phone use and exposure from base station signals is duration of exposure. While mobile phones are used intermittently with exposure duration seldom exceeding 1 h per day, exposure to base stations is continuous and for up to 24 h a day. It has also to be mentioned that the exposure of mobile phone users is in the near field and localized at the head region, while base stations expose the whole body to the far field. Strictly speaking exposure from mobile phones and their base stations have almost nothing in common except for the almost equal carrier frequency that is likely of no importance for biological effects.

Concerning reconstruction of exposure to base station signals there is no greater difficulty than for retrospective assessment of exposure to mobile phones. It is not always necessary to determine exposure precisely. For epidemiological investigations it often suffices to have a certain gradient of exposures. As long as any two persons can be differentiated along such a gradient epidemiological investigations can and should be carried out.

There are seven field studies of wellbeing and exposure to base station signals available to date. Two were in occupational groups working in a building below [11] or below as well as opposite a building with a roof-mounted base station antenna [10]. The other five were in neighbors of base stations: Santini et al. [5,6], Navarro et al. [8], Hutter et al. [9], Blettner et al. [7], and Thomas et al. [12]. Studies had different methodologies with the least potential for bias in the studies of Hutter et al. [9] and Blettner et al. [7]. All other studies could be biased due to self-selection of study participants. One study explored personal dosimetry during 24 h [12] but results were inconclusive due to insufficient power and omission of nighttime measurements. The study of Blettner et al. [7] had an interesting design with a first phase in a large population based representative sample and a second phase with individual measurements in the bedrooms of participants that were a subgroup of the larger sample. Unfortunately this second sample did not contain a sufficiently large fraction of individuals with relevant exposure (99% had bedside measurements below 0.3 mW/m^2).

Despite some methodological limitations of the different studies there are still strong indications that long-term exposure near base stations affects wellbeing. Symptoms most often associated with exposure were headaches, concentration difficulties, restlessness, and tremor. Sleeping problems were also related to distance from base station or power density, but it is possible that these results are confounded by concerns about adverse effects of the base station, or more generally, by specific personality traits. While the data are insufficient to delineate a threshold for adverse effects the lack of observed effects at fractions of a mW/m^2 power density suggests that, at least with respect to wellbeing, around 0.5–1 mW/m^2 must be exceeded in order to observe an effect. This figure is also compatible with experimental studies of wellbeing that found effects at 2.7 and 10 mW/m^2.

There are regular media reports of an unusually high incidence of cancer in the vicinity of mobile phone base stations. Because there are several hundred thousand base stations operating all over the world some must coincide by chance with a high local cancer incidence. Regionally cancer incidence has a distribution with an overdispersion compared to the Poisson distribution. Overdispersion is predominantly due to variations in the distribution of age and gender. Therefore, a much higher number of cases than expected from average incidences can occur by chance. Unfortunately there are no multi-regional systematic investigations of cancer incidence related to mobile phone base stations available to date. Only studies in a single community, one in Bavaria [14] and one in Israel [15], have been published that reported a significantly increased incidence in an area of 400 and 350 m around a base station, respectively. Although incidence in proximity to the base station strongly exceeded the expected values and was significant even considering overdispersion in the case of the Neila study in Bavaria, still no far reaching conclusions can be drawn due to the ecological nature of the studies. However, both studies underline the urgent need to investigate this problem with an appropriate design. Neubauer et al. [30] have recommended focusing initially on short-term effects and 'soft' outcomes given the problems of exposure assessment. However, as has been mentioned previously, the problems of exposure assessment are less profound as often assumed. A similar approach as chosen in the study of leukemia around nuclear power plants [31] could be applied also for studying cancer in relation to base station exposure. Such a case–control design within areas around a sufficiently large sample of base stations would provide answers to the questions raised by the studies of Eger et al. [14] and Wolf and Wolf [15].

In 2003 the so-called TNO study [19] had received wide publicity because it was the first experimental investigation of short-term base station exposure in individuals that rated themselves sensitive to such signals. A lot of unfounded criticism was immediately raised such as complaints about the limited sample size and the not completely balanced design. But also valid arguments have been put forward. The consecutive tests with all experimental conditions presented one after the other could result in sequential effects that may not be completely removed by balancing the sequence of exposures. In several countries follow-up studies were initiated two of which have already been published [21,23]. One of these experiments partly supported the TNO study the other found no effect. While the study of Regel et al. [21] closely followed the conditions of the previous experiment only avoiding the shortcomings of a sequential within-day design and improvements by including two intensities of UMTS exposure, the study of Eltiti et al. [23] had a different procedure and included physiological measurements. Regel et al. [21] applied the same questionnaire as has been used in the TNO study. Because non-sensitive participants and sensitive participants during sham exposure (despite their almost 10 years younger age) reported considerably lower wellbeing,

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it is possible that the experimental setup was more adverse and imposed too much stress such that these conditions confounded the effect of the base station exposure. Results of the other replication experiment of Eltiti et al. [23] may be compromised by an imbalance in the sequence of experiments with more sensitive participants receiving UMTS exposure in the first session. Hence, based on available evidence, it cannot be firmly decided whether such weak signals as applied in these experiments to simulate short-term base station exposure affects wellbeing.

Concerning animal experiments and in vitro investigations the data base is insufficient to date. While in vivo exposure of Wistar albino rats [26] imply an induction of oxidative stress or an interaction with antioxidant cellular activity, in vitro experiments [27] found no indication of cellular stress in human glioblastoma cells and fibroblasts. While some may be inclined to attribute effects in the low-dose range to experimental errors there is the possibility that the characteristics of the exposure that are relevant for an effect to occur simply vary in the experiments and lead to ambiguous results. As long as these decisive features of the exposure (if they actually exist) are unknown and in particular the type and components of low-frequency modulation vary across experiments, it is impossible to coherently evaluate the evidence and to come to a science based conclusion.

Overall results of investigations into the effects of exposure to base station signals are mirroring the broader spectrum of studies on handsets and on RF-EMF in general. There are indications from epidemiology that such exposures affect wellbeing and health weakly supported by human provocation studies and an inconclusive body of evidence from animal and in vitro studies.

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Review

Long-term exposure to magnetic fields and the risks of Alzheimer's disease and breast cancer: Further biological research

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Abstract

Objective: Extremely low frequency (ELF) and radio frequency (RF) magnetic fields (MFs) pervade our environment. Whether or not these magnetic fields are associated with increased risk of serious diseases, e.g., cancers and Alzheimer's disease, is thus important when developing a rational public policy. The Bioinitiative Report was an effort by internationally recognized scientists who have spent significant time investigating the biological consequences of exposures to these magnetic fields to address this question. Our objective was to provide an unbiased review of the current knowledge and to provide our general and specific conclusions. **Results:** The evidence indicates that long-term significant occupational exposure to ELF MF may certainly increase the risk of both Alzheimer's disease and breast cancer. There is now evidence that two relevant biological processes (increased production of amyloid beta and decreased production of melatonin) are influenced by high long-term ELF MF exposure that may lead to Alzheimer's disease. There is further evidence that one of these biological processes (decreased melatonin production) may also lead to breast cancer. Finally, there is evidence that exposures to RF MF and ELF MF have similar biological consequences. **Conclusion:** It is important to mitigate ELF and RF MF exposures through equipment design changes and environmental placement of electrical equipment, e.g., AC/DC transformers. Further research related to these proposed and other biological processes is required.
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Keywords: Extremely low frequency (ELF); Magnetic fields (MFs); Amyloid beta (Aβ); Melatonin; Alzheimer's disease (AD)

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1. Introduction

In this review, we emphasize (a) two proposed biological models "explaining" the apparent relationship between high, long-term exposure to extremely low frequency (ELF) magnetic fields (MFs) and Alzheimer's disease (AD), one of which also relates to breast cancer and (b) areas of biological research needed to confirm or refute these models. Prior to this discussion, we provide the conclusions from our detailed review chapter (Section 12: Davanipour and Sobel [1]) in the Bioinitiative Report [2] related to epidemiologic research, which initially identified these relationships. We refer the reader to Section 12 and supporting, peer-reviewed papers for details of the epidemiologic studies discussed in that section. Other papers in this issue of Pathophysiology (e.g., on the stress response and DNA strand breaks) demonstrate that exposures to ELF MF and radio frequency (RF) MF often have the same biological consequences.

2. Epidemiologic studies presented in the Bioinitiative Report related to Alzheimer's disease and breast cancer

The conclusions reached from our detailed review of the literature in Section 12 in the Bioinitiative Report (see references for URL) on long-term significant ELF MF exposure and Alzheimer's disease and breast cancer are provided below [1]. The section references below refer to sub-sections of Section 12 of the Bioinitiative Report.

Melatonin production (Section II). Eleven of the 13 published epidemiologic residential and occupational studies are considered to provide (positive) evidence that high long-term ELF MF exposure can result in decreased melatonin production. The two negative studies had important deficiencies which may certainly have biased the results. Thus, there is sufficient evidence to conclude that long-term relatively high ELF MF exposure can result in a decrease in melatonin production. It has not been determined to what extent personal characteristics, e.g., medications, interact with ELF MF exposure in decreasing melatonin production.

2.1. Alzheimer's disease

Section 12 of the Bioinitiative Report provides the details of the following conclusions.

- There is initial evidence that (i) a high level of peripheral amyloid beta, generally considered the primary neurotoxic agent when aggregated, is a risk factor for AD and (ii) medium to high MF exposure can increase peripheral amyloid beta. High brain levels of amyloid beta are also a risk factor for AD and medium to high MF exposure to brain cells likely also increases these cells' production of amyloid beta (Section IIIA).
- There is considerable *in vitro* and animal evidence that melatonin protects against AD. Therefore, it is certainly possible that low levels of melatonin production are associated with an increase in the risk of AD (Section IIIB).
- There is strong epidemiologic evidence that long-term exposure to ELF MF is a risk factor for AD. There are seven studies of ELF MF exposure and AD that met our inclusion criteria. Six of these studies are more of less positive and only one is negative. The negative study has a serious deficiency in ELF MF exposure classification which results in subjects with rather low exposure being considered as having significant exposure. Several published studies were excluded from further consideration due to serious deficiencies, primarily diagnostic inaccuracy (e.g., use of death certificates for diagnosis of AD) and/or serious exposure assessment problems. These latter studies likely had risk estimated seriously biased towards the null hypothesis of no risk. It should be noted, however, that even some of these studies were positive (Sections IIIC and IIID).

2.2. Breast cancer

There is sufficient evidence from *in vitro* and animal studies, from human biomarker studies, from occupational and light at night case-control studies, and the only two longitudinal studies with appropriate collection of urine samples to conclude that high ELF MF exposure may certainly be a risk factor for breast cancer (Section IV). Note that at the time the Bioinitiative Report was made public, there was only one longitudinal study with appropriate collection of urine samples. There are now two such studies [3,4].

Seamstresses. Seamstress is, in fact, one of the most highly ELF MF exposed occupations, with exposure levels generally well above 10 mG over a significant proportion of the workday. Seamstresses have been consistently found to be at higher risk of Alzheimer's disease and breast cancer. This occupation deserves specific attention in future studies. We are unaware of any measurements of RF MF among seamstresses (Section V and throughout Section 12).

3. Biological hypotheses relating ELF MF exposure to Alzheimer's disease and breast cancer

Two biological hypotheses are discussed. The first one relates ELF MF exposure to increased amyloid beta (Aβ) production and subsequent development of AD. The second one relates ELF MF exposure to decreased melatonin production. Decreased melatonin production appears to have differing deleterious consequences related to AD and breast cancer development.

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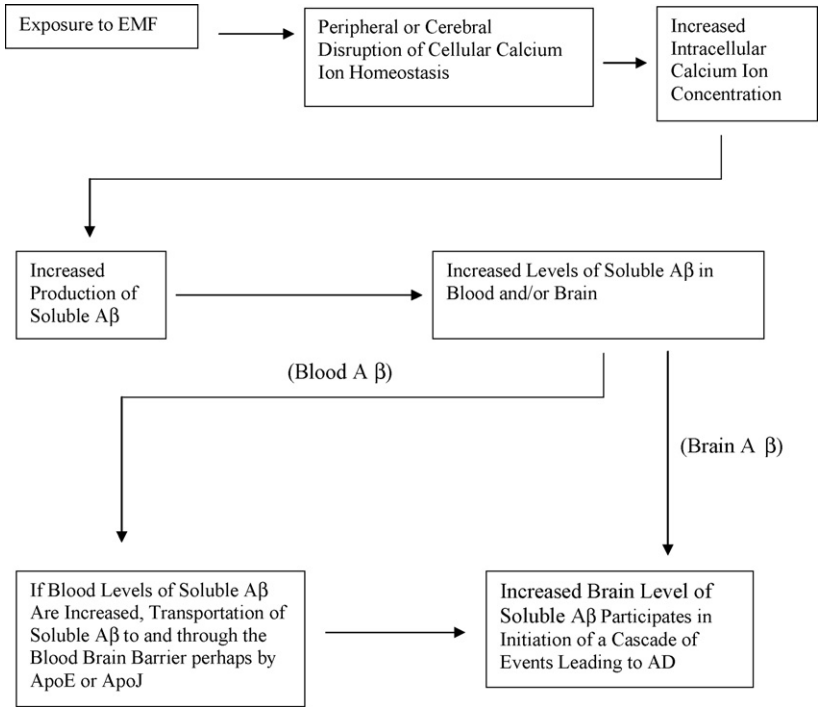

Fig. 1. Hypothesized biological pathway from MF exposure to AD Development (from Sobel and Davanipour [5]).

3.1. ELF MF exposure and peripheral and brain production of amyloid beta (Fig. 1)

The ELF MF exposure and increased amyloid beta hypothesis was developed by Sobel and Davanipour as a result of our initial findings that long-term ELF MF occupational exposure was a risk factor for AD [5] (see Fig. 1). Seamstress was the most common occupation among subjects with AD in the five databases we investigated [6–8]. ELF MF exposure among seamstresses had not been measured prior to our 1995 study [6]. Beginning in 1994, we measured a very large number of seamstresses working in either a factory setting or individually. Their exposures were very high, particularly when using an industrial sewing machine. The highest exposures were, however, not to the brain, because the motor on industrial machines is located at the knees. The motor or AC/DC transformer in home sewing machines is in the machine arm located near the operator's chest and right arm. This peripheral exposure led us to consider how peripheral ELF MF exposure might be associated with development of amyloid plaques in the brain.

Our biologically plausible hypothesis relating MF exposure to AD is based on the independent work of many researchers in several different fields. Details and references are provided in Sobel and Davanipour [5]. Briefly, the hypothesized process involves increased peripheral or brain production of Aβ as a result of MF exposure causing voltage-gated calcium ion channels to be open longer than normal. This results in abnormally high intracellular levels of calcium ions which in turn results in the production of Aβ. The resulting Aβ is quickly secreted into the blood. If peripheral, the Aβ is then transported to and through the blood–brain barrier, perhaps best chaperoned by the ε4 isoform of apolipoprotein E (apoE). (Note that this might be one reason why the ε4 isoform is a risk factor for AD.) Fig. 1 provides a schematic outline of the hypothesis. Each step in the proposed pathway is supported by *in vitro* studies.

At the time of publication of this hypothesis, no human studies related to this hypothesis had been conducted. There are now two groups that have published relevant studies, without apparently any knowledge of our hypothesis—or at least no reference to the hypothesis: (1) high levels of peripheral $A\beta_{1-42}$, the more neurotoxic version of Aβ, has been found to be a risk factor for AD [9,10]; acute exposure to ELF MF increases peripheral Aβ [11]. Details may also be found in the Bioinitiative Report (Section IIIA) [1].

3.2. Melatonin—background

Melatonin is found in every cell of the body and readily crosses the blood–brain barrier. It scavenges reactive oxygen species (ROS) at both physiologic and pharmacologic concentrations. In the literature, "physiologic" refers to blood level concentrations of melatonin, while "pharmacologic" indicates 2–3 orders of magnitude higher concentration. Recently, intracellular levels of melatonin, especially within the nucleus, have been shown to be naturally at "pharmacologic" levels for all cellular organelles studied to date [12,13].

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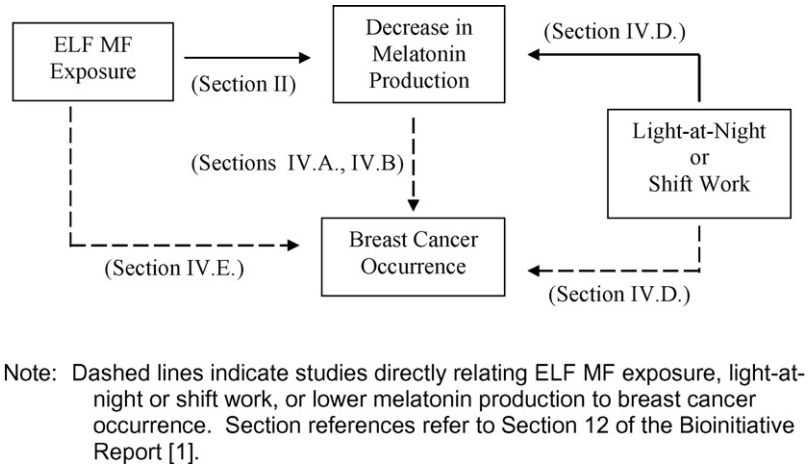

Fig. 2. Outline of the evidence that ELF MF exposure causes breast cancer through decreases in melatonin production—with section references to Section 12, Bioinitiative Report [1]. Note: Dashed lines indicate studies directly relating ELF MF exposure, light-at-night or shift work, or lower melatonin production to breast cancer occurrence.

3.3. Low melatonin production and Alzheimer's disease

Numerous *in vitro* and animal studies indicate that melatonin may be *protective* against AD and thus low or lowered melatonin production may be a risk factor for AD. These studies have found that melatonin has the following effects:

- Inhibition of the neurotoxicity and cytotoxicity of Aβ, including in mitochondria [14–19];
- Inhibition of the formation of β-pleated sheet structures and Aβ fibrils [20–25];
- Reversal of the profibrillogenic activity of apolipoprotein E ε4, an isoform conferring increased risk of AD [21];
- Inhibition of the oxidative stress *in vitro* and in transgenic mouse models of AD, if given early [23,26,27], but not necessarily if given to old mice [28];
- Increase in survival time in mouse models of AD [23];
- Reduction of oxidative stress and of proinflammatory cytokines induced by $A\beta_{1-40}$ in rat brain *in vitro* and *in vivo* [29–31];
- Decrease of the prevalence of $A\beta_{1-40}$ and $A\beta_{1-42}$ in the brain in young and middle aged mice [32];
- Improvement of memory and learning in rat models of AD pathology [33,34], but not necessarily in Aβ-infused rat models [35].

Note that transgenic mouse models of AD mimic senile plaque accumulation, neuronal loss, and memory impairment. There have been several reviews, e.g., [36–39]. Thus, chronic low levels of melatonin production may be etiologically related to AD incidence [40].

3.4. Low melatonin production and breast cancer

See Fig. 2 for a diagram of the discussed relationships between ELF MF exposure and breast cancer risk.

In vitro studies related to prevention of oxidative damage. Well over 1000 publications have found that melatonin neutralizes hydroxyl radicals and reduces oxidative damage. For reviews see Tan et al. [41] and Peyrot and Ducrocq [42]. Melatonin has also been shown to act synergistically with vitamin C, vitamin E and glutathione [43] and stimulates the antioxidant enzymes superoxide dismutase, glutathione peroxidase and glutathione reductase [44]. Furthermore,

- melatonin neutralizes hydroxyl radicals more efficiently than does reduced glutathione [45,46];
- melatonin reduces oxidative damage to macromolecules in the presence of free radicals [47,48] due at least to its free radical scavenging properties [49];
- melatonin increases the effectiveness of other antioxidants, e.g., superoxide dismutase, glutathione peroxidase, and catalase [50–54];
- melatonin has protective effects against ultraviolet and ionizing radiation [55–57];
- melatonin has been found to be a more potent protector from oxidative injury than vitamin C or vitamin E (micromoles/kg) (for a review of the evidence, see: Tan et al. [43];
- melatonin was also found *in vitro* to scavenge peroxyl radicals more effectively than vitamin E, vitamin C or reduced glutathione [58], although melatonin is not a very strong scavenger of peroxyl radicals [49].

Animal studies of melatonin and mammary tumor prevention. Several studies have found that melatonin inhibits the incidence of mammary tumors in laboratory animals either prone to such tumors or exposed to a carcinogen (e.g., [50–63]). Tan et al. [64,65] found that melatonin at both physiological and pharmacological levels protected Sprague–Dawley rats from safrole induced liver DNA adduct formation. Melatonin and retinoic acid appear to act synergistically in the chemoprevention of animal model tumors [66] and *in vitro* systems [67].

Melatonin prevents oxidative DNA damage by estradiol and radiation. Karbownik et al. [68] found that melatonin

protects against DNA damage in the liver and kidney of male hamsters caused by estradiol treatment. Several studies have found that laboratory animals are protected by melatonin from lethal doses of ionizing radiation (e.g., [69–71]). Vijayalaxmi et al. [70] and Karbownik et al. [71] also investigated markers of oxidative DNA damage and found significant decreases in these markers in the melatonin treated animals.

Melatonin: Scavenger of $^{\bullet}OH$ and Other ROS. Melatonin is a powerful, endogenously produced scavenger of reactive oxygen species (ROS), particularly the hydroxyl radical ($^{\bullet}OH$). Other ROS which melatonin scavenges include hydrogen peroxide (H_2O_2), nitric oxide ($NO^{\bullet}$), peroxynitrite anion ($ONOO^-$), hypochlorous acid (HOCl), and singlet oxygen ($^1O_2$) [50,72–75]. $^{\bullet}OH$ is produced at high levels by natural aerobic activity. ROS are also produced by various biological activities or result from certain environmental and lifestyle (e.g., smoking) exposures. $^{\bullet}OH$ is the most reactive and cytotoxic of the ROS [76]. $^{\bullet}OH$ appears not to be removed by antioxidative enzymes, but is only detoxified by certain direct radical scavengers such as melatonin [77].

4. Discussion and future research

Other papers in this special issue of Pathophysiology provide evidence that RF MF exposure and ELF MF exposure may have similar biological consequences.

We primarily limit our discussion of future research to studies in humans with experimental medicine components, emphasizing the latter. However, we initially discuss limiting exposures.

It should be noted that ELF MF exposure may also be associated with other cancers. This may be because of the decrease in melatonin production and melatonin's varying antioxidant, anti-inflammation, and immune response enhancement properties.

4.1. Epidemiologic studies

The incidence rates of Alzheimer's disease and breast cancer are increasing. These increases are certainly in part due to our living longer, at least for AD, if not better lives. However, environmental exposures are likely to play important roles. At the same time, ELF and RF MF exposure is becoming more and more common in our world. In our three published studies of MF and AD, approximately 7.4–12.0% of the cases and 3.4–5.3% of the controls had primary occupations associated with medium or high ELF MF exposure [6–8]. Many more subjects may have had exposures from sources generally not identified in epidemiologic studies, because individualized 'on-site' exposure assessment is usually not feasible. We give two examples coming from 'onsite' inspections we have performed: a subject who had developed amyotrophic lateral sclerosis (ALS) had spent many years with a 75 mG ELF MF exposure due to having his foot on a deadbolt lock/unlock foot devise for his office door under his desk; a subject who had developed AD who spent over 25 years sitting at his home desk for at least 4 h per day in a chair backed up to a wall with a fuse box directly on the other side of the wall which produced a very high ELF MF exposure to his back and head. (Note that there is also significant epidemiologic evidence that ELF MF exposure is a risk factor for ALS.) The frequencies of such exposures in studies are unknown.

As is often the case, more research is required. However, the designs of this future research should be informed and directed by the results of previous research. Future epidemiologic studies should use subjects for whom it is unequivocally known that the ELF MF and/or RF MF exposure is high and matched subjects for whom such exposure is known to be low. Matching criteria should include age, gender, and residential environment so as to at least partially exclude other exposures.

There should be additional studies related to the levels of production of peripheral amyloid beta, particularly $A\beta_{1-42}$, and melatonin, on the one hand, and both MF exposure and the risk of AD, on the other hand. Such studies need to be able to investigate the possible associations between peripheral amyloid beta and melatonin levels and both earlier/concurrent MF exposure and subsequent development of AD. Similar studies need to be carried out for breast cancer, excluding the amyloid beta component. This effort will likely require both retrospective and longitudinal studies. There are only two known longitudinal studies [3,4] which collected urine samples at baseline so that overnight premorbid melatonin production was reliably estimated. These studies found an association between low melatonin production and breast cancer. These studies may also be able to provide important additional information if it is possible to determine MF exposures with reasonable accuracy and follow-up AD status on a sufficient number of participants.

Case-control studies of melatonin as a risk factor for AD and breast cancer are hampered by the fact that biological sequelae of both AD and breast cancer result in a decline of melatonin production to an unknown extent. (In breast cancer patients, there is a melatonin production rebound when tumors are surgically removed. In AD patients, the production of serotonin, the precursor of melatonin, is decreased and noradrenergic regulation becomes dysfunctional [78].) However, melatonin production is partially under genetic control. We have conducted a study of relatively healthy members of nuclear families and melatonin production (DOD Congressionally Directed Medical Research Program Grant: DAMD17-00-1-0692). The production of melatonin of the mother was successfully modelled as a function of the melatonin of a daughter, after adjusting for both the daughter's age and the influence of the father. This work allows for the design of case-control studies of the influence of long-term MF exposure on both melatonin production and the risks of breast cancer and AD.

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4.2. ELF and/or RF MF exposure mitigation

It is also vital to mitigate both the extent of MF exposure and the effects of such exposure. Mitigation means efforts to both locate and shield or move the sources of MF away from individuals and design equipment which produces lower levels of MF. Little effort has apparently been spent on design issues. There are simple things that can be done. For example, almost all AC/DC transformers emit about 75 mG ELF MF fields. The exception, in our experience, has been a few transformers for Apple laptops measured about 10 years ago. AC/DC transformers are now everywhere, specifically under and around office desks and in nearly every room in a residence, often near the heads of beds. Maximizing one's distance from a transformer is important, because the strength of the MF field drops off with the square or cube of the distance from the source.

Seamstress is a very common profession and being a seamstress is clearly a risk factor for AD and quite possibly for breast cancer also. Seamstresses experience higher ELF MF exposure than members of almost any other profession. Older industrial sewing machines are extremely common all over the world. They produce extremely strong MFs, but it is possible to design "covers" for the motor to interfere with these fields, much as "headphones" can mitigate sound waves. Newer computer driven home sewing machines produce MF because of the AC/DC transformer. These transformers are placed in the arm of the machine, which results in high MF exposure to the operator. Simply by connecting the transformer to the machine by an electrical cord about three or more feet from the operator would mitigate a significant percentage of the MF exposure.

4.3. Biological mechanisms/experimental medicine research

We argue that, to the extent possible, research should now be conducted in humans. We list the following research questions as important examples of studying the biological effects of ELF and/or RF MF exposure:

1. Generation of peripheral amyloid beta
   a. Determination of intracellular Ca^{2+} ion concentration changes as a consequence of ELF or RF MF exposure.
   b. Measurement of the amount of $A\beta_{1–42}$ and $A\beta_{1–40}$ produced by and secreted from cells.
      i. This could be done at least by measuring blood levels of amyloid before and after ELF and/or RF MF exposure.
      ii. Perhaps there are more sophisticated experimental designs.
   c. Determination of which cell types in fact produce more amyloid beta after or during ELF and/or RF MF exposure.
   d. Determination of the dose response relationship(s) between ELF and/or RF MF exposure and cellular amyloid beta production.
   e. Measurement of the accumulation of amyloid beta in the brain, perhaps using PET scans [79,80].
2. Decrease in melatonin production

   Note: it is known that the pineal gland, the primary source of melatonin, has a tendency to become calcified and, perhaps, this is the reason why generally there is a reduction of melatonin production during aging.
   a. Determination of the extent of intracellular calcium within the pineal gland as a result of acute ELF and/or RF MF exposure.
   b. Determination of the extent of calcification of the pineal gland as a result of varying levels of long-term ELF and/or RF MF exposure.

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Reproductive and developmental effects of EMF in vertebrate animal models

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Abstract

This paper reviews the literature data on the effects of electromagnetic fields (EMF), in the reproductive organs as well as in prenatal and postnatal development of vertebrate animals. Review articles which have been published till 2001, regarding the reproductive and developmental effects of the entire range of frequency of electromagnetic fields, were surveyed. Experimental studies which were published from 2001 onwards were summarized. Special focus on the effects of radiofrequencies related to mobile communication in the above mentioned topics has been made. According to the majority of the investigations, no strong effects resulted regarding the exposure to EMF of mobile telephony in the animal reproduction and development. However further research should be done in order to clarify many unknown aspects of the impact of EMF in the living organisms.
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Keywords: Electromagnetic fields (EMF); Mobile phones; Teratology; Endometrium; Testis

1. Introduction

During the 20th century, the exposure to electromagnetic fields (EMF) became an important source of concern about the possible effects in the living organisms. The artificial sources of electromagnetic radiation have risen tremendously because of the ongoing needs on electricity, telecommunications, and electronic devices. In this context, World Health Organisation (WHO) established in 1996 the International EMF project in order to assess health and environmental effects of exposure to EMF in the frequency range from 0 to 300 GHz. For the purpose of this paper this range will be divided into static (0 Hz), extremely low frequency (ELF > 0–300 kHz), intermediate frequencies (IF > 300–10 MHz) and radiofrequency (RF 10 MHz–300 GHz) fields [J. Juutilainen, Developmental effects of electromagnetic fields, Bioelectromagnetics 7 (2005) S107–S115]. The mobile phone technology is based on radiofrequency radiation with transmission of microwaves carrying frequencies between 880 and 1800 MHz [P.A. Valberg, T.E. van Deventer, M.H. Repacholi, Workgroup report: base stations and wireless networks-radiofrequency (RF) exposures and health consequences, Environ. Health Perspect. 115 (2007) 416–424].

The mobile telephony revolution took place in the last decade. There is an increasing number of cell phone users all over the world. Also, new technologies which use the spectrum of high frequency emissions are incorporated in many aspects of telecommunications. As a consequence, there is a lot of interest about the possible effects of the radiation emitted from the machines which are engaged in the telephony such as hand phones, base stations and transmitters.

The biological effects of EMF have been and are being investigated on different levels of organization. On the level of human populations, epidemiological studies are used whereas, on the level of individuals human, animal and plant *in vivo* experiments are carried out. Furthermore, on the level of organs, tissues and cells *in vitro* investigations are employed. Finally, on the sub-cellular level, biochemical and molecular techniques are utilized.

From another point of view, many studies have been carried out or are in progress about the various effects of radiation emissions regarding the behaviour, cancer, central nervous system, sleep, children, cardiovascular system, immune function, reproduction and development [3].

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The present paper will focus on the existing data about the reproductive and developmental effects of EMF in vertebrates. Reproduction is a critical function of the organisms and involves two body systems the male and female genital system. The development comprises a series of events which begins with fertilization, continues with implantation, embryonic growth and terms with sexual maturity. In the context of systematic zoology, the vertebrates are close to the humans. Therefore, the animal studies could provide useful information on the comprehension of interaction of EMF with the living organism and on the possible commonality with the humans.

The biological effects of EMF of interest can be broadly grouped into thermal and non-thermal [4]. The thermal effects are associated with local heat production just like the mechanism of a microwave oven. The non-thermal mechanism is triggered by an amount of energy absorption, which is not directly associated with temperature change but rather to some other changes produced in the tissues.

The goal of this paper is to present the up to date available data about the EMF and their potential effects on reproduction and development, filling the gap of information from the most recent published reviews. All the bibliographic data which will be presented were collected exclusively from scientific journals published in English and partially in other languages. The survey includes studies which were published from 2001 onward. The studies which relate to the impact of mobile phone electromagnetic fields will be presented thoroughly and independently from the date of their publication.

2. Historical background

The first paper which I found in the medical literature, regarding the effects of EMF on the development of vertebrates, was published in 1893 in an anatomical journal from Windle [5]. The author summarized the observations of three scientists and added his own about the effects of electricity on the chicken embryos. Two years later the same author [6], published an account on the effects of electricity and magnetism on development.

In 1980 two papers were published about the biological effects of microwave radiation. Cook et al. [7] published a comprehensive survey regarding the very early research on the biological effects of electromagnetic fields. The early work on short waves from 1885 to 1940 was presented. Following, the authors summarized the available data from 1940 to 1960. Leach [8] provided an account on the genetic, growth and reproductive effects of microwave radiation including early studies in this field that were published from 1959 to 1979. The majority of revised papers dealt with animals. Later, Algers and Hennichs [9] summarized the biological effects on vertebrates, of electromagnetic fields where the frequency did not exceed 100 Hz. The authors included many studies about the impact of EMF on farm animals. The same year, a specialized review was published on the effects of non-ionizing radiation on birds [10].

Berman et al. [11], presented the results of a large multinational experimental effort (Henhouse project) regarding the low frequency EMF effects on chick embryos. Juutilainen [12], Chernoff et al. [13], Brent et al. [14] presented detailed reviews of the literature about the effects on reproduction related to low frequency EMF.

Jensh [15] reviewed behavioral teratologic studies using microwave radiation with special interest to continuous wave (CW) 915, 2450, or 6000 MHz radiation.

Verschaeve and Maes [16] reviewed the genetic, carcinogenic and teratogenic effects of RF (300 MHz–300 GHz). Regarding the effects on reproduction and teratogenesis, studies from 1961 to 1991 were surveyed. The majority of these experimental studies dealt with the exposure of animals at 2.45 GHz. The same year, Huuskonen et al. [17] reported on the teratogenic and reproductive effects of low frequency (0–100 kHz) magnetic fields associated with the use or transmission of electric power or emitted from video display terminals. The animal studies that were surveyed, have been published from 1987 to 1997 regarding the effects of alternating magnetic fields on prenatal development of rats and mice. In the same paper, studies on the effects of prenatal exposure of alternating magnetic fields on postnatal development were included. Brent [18] provided a thorough review of *in vivo* and *in vitro* studies on the reproductive and teratologic effects of low frequency EMF. The survey of reproductive effects has involved studies with chick embryos, chickens, cows, mice, and rats from 1969 to 1996. O'Connor [19] recorded the intrauterine effects in animals exposed to radiofrequency and microwave fields with a special feature. The SAR of the surveyed studies was above the limit of 0.4 W/kg.

Experimental studies on the teratologic effects or developmental abnormalities from exposure to RF electromagnetic fields in the range 3 kHz–300 GHz were reviewed from Heynick and Merritt [20]. The review included investigations with insects, birds (chicken, quails, turkeys) and mammalian species (mice, rats) as well as non-human primates which appeared from 1974 to 2000. A brief critical review on the developmental effects of extremely low frequency (ELF) electric and magnetic fields provided by Juutilainen [21]. Löscher [22] published a survey of the effects of radiofrequency electromagnetic fields on production, health and behaviour of farm animals.

Juutilainen [1] reported on the effects of EMF on animal development. In his review, he surveyed specific topics such as the Henhouse project, the interaction of LF-IMF EMF with known teratogens, and the behavioral teratology of RF. Saunders and McCaig [23] summarized the possible effects on prenatal development of physiologically weak electric fields induced in the body by exposure to extremely low frequency electromagnetic fields and of elevated temperature levels that might result from exposure to radiofrequency (RF) radiation.

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Table 1
Overview of investigations on EMF effects on animal genital system.

Animal species	Exposure frequency	Exposure parameters	Exposure duration	Endpoint	Results	Comments	Reference
Mouse Swiss	50 Hz	25 mT	Continuous 90 days	Effects on reproductive ability	No effect on the fertility of male and female mice. The ovarian weight was significantly increased		[27]
Mouse CD1 (BALB/c X DBA/2)	60 Hz	2 mT	Continuous for 72 h or 8 h/day for 10 days	Sperm morphology	No statistically differences were observed	Two groups were treated with mitomycin C. Sperm abnormalities were found in the group exposed versus the group treated with mitomycin C alone	[28]
Mouse BALB/c	60 Hz	0.1 or 0.5 mT	24 h/day for 8 weeks	Germ cell apoptosis in the testes	No significant changes in testicular weights. Decrease of normal seminiferous tubules. Increase of the germ cell death		[29]
Rat Sprague–Dawley	60 Hz	5, 83.3, 500 mT	Continuous 21 h/day from day 6 of gestation to day 21 of lactation	Spermatotoxicity and reproductive dysfunction inthe F1 offspring	No detectable alterations in offspring spermatogenesis and fertility		[30]
Rat Sprague–Dawley	50 Hz	$25 \pm 1\ \mu T$	Continuous for 18 weeks	Effects on sperm count, weights of testes, seminal vesicles, preputial glands	No effect on the weight of testes. Significant reduction of the weight of seminal vesicles and preputial glands. Significant reduction in sperm count		[31]
Rat Sprague–Dawley	50 Hz	1.35 ± 0.018 mT	2 h/day, 7days/week for 2 months	Sperm count, morphological changes of testes	No significant alterations were observed	Funding not mentioned	[32]
Rat Wistar albino♀♂	50 Hz	1 mT (mean value)	3 h/day for 50 or 100 days	Morphological evaluation of uterus and ovaries	Ultrastructural alterations in germinal epithelium of ovaries in the experimental group (50 days) as well as in tunica albuginea (100 days)	Ambiguous observations in the uterus	[33]
Rat Sprague–Dawley♂♀	20 kHz	6.25 mT	8 h/day, 5 days/week for 90 days	Histopathological examination of various organs	No differences were seen in testis and ovary		[34]

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Table 1 (*Continued*)

Animal species	Exposure frequency	Exposure parameters	Exposure duration	Endpoint	Results	Comments	Reference
Rat Wistar ♂♀	50 Hz		3 weeks *in utero* and 5 weeks postnatal	Testes	Morphological changes in the boundary tissue of the seminiferous tubules		[35]
Rat Sprague–Dawley♀♂	20 kHz sine waves	6.25 mT	8 h/day for 12 or 18 months	Histopathological examination of various organs	No differences were seen in testis and ovary		[36]
Rat Wistar	30–300 GHz	>0.3 mW/cm^2	30 min for 63 days	Spermatogenesis	Morphological changes in spermatozoa	Scanty data presentation	[37]
Rat Wistar	50 Hz		8 h/day for 8 months	Histological evaluation of testes	Mean seminiferous tubule diameter and testicular weight were significantly lower in exposed group. Histologic damage score was threefold in experimental group versus control		[38]

A special topic, the effects of EMF from power lines on avian reproductive biology, was reviewed by Fernie and Reynolds [24]. Krewski et al. [25], reviewed studies referring to various disciplines regarding the effects of RF. The included literature was published between 2001 and 2003. A novelty of this paper, was a discussion of the reports of various authorities and committees about the potential health risks associated with exposure to RF fields. A gap in the literature regarding the biological effects of EMF in the intermediate frequency range was covered by the review of Shigemitsu et al. [26].

During the last decade, many reports from authorities (local, national and international) and expert panels have been uploaded on the web [2].

It is suggested that the reader refer to the above-mentioned review articles and electronic addresses, in order to assemble a more complete and detailed view of the biological effects of EMF.

3. Male genital system

The testes are very important organs situated externally to the body and enclosed by the scrotum. The testicular parenchyma is the site of an intense proliferation and differentiation of the germinal cells that will become the sperm cells. The testes are very sensitive to temperature variations and for this reason the scrotum, which contains the testicular parenchyma, has a specialized contractile structure.

Studies that have evaluated EMF effects (mainly LF) on the genital systems of the vertebrates are summarized in Table 1.

Regarding mobile telephony, the first study conducted by Dasdag et al. [39] investigated whether there are adverse effects due to microwave exposure emitted by cellular phones in male Wistar albino rats. The animals ($n = 18$) were divided in three groups (control, standby exposed group, speech exposed group). Specific energy absorption rate (SAR) was 0.141 W/kg. Rats in the experimental groups were exposed for 2 h/day for 1 month in standby position, whereas phones were turned to the speech position three times for 1 min. The decrease of epididymal sperm counts in the speech groups was not found to be significant. Differences in terms of normal and abnormal sperm forms were not observed. Histological changes were especially observed in the testes of rats in the speech group. Seminiferous tubular diameter of rat testes in the standby and speech groups was found to be lower than the sham group. Rectal temperatures of rats in the speech group were found to be higher than the sham and standby groups. The rectal temperatures of rats before and after exposure were also found to be significantly higher in the speech group.

The same group of authors [40], failed to reproduce the results of their previous work. Sixteen Sprague–Dawley rats were separated into two groups (control, experimental). They were exposed to 890–915 MHz pulsed wave (PW) daily for

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20 min/day for 1 month. For 250 mW average radiated power, SAR was 0.52 W/kg. No differences were observed in the percentages of epididymal normal and abnormal sperms, the epididymal sperm count, as well as in the seminiferous tubule diameter between control and experimental groups. Also, the testicular biopsy score as evaluated by Johnson's scale did not differ significantly.

Aitken et al. [41] assessed the testis of mice irradiated with 900 MHz in a waveguide, with an exposure condition SAR 90 mW/kg for 7 days at 12 h/day. The authors did not observe abnormalities regarding the sperm number, morphology and vitality. However, they reported significant damage to the mitochondrial genome as well as to the nuclear-globin locus.

Results similar to a previous study [39] regarding the diameter of the seminiferous tubules of rat testes were obtained by Ozguner et al. [42]. During the experiment, 20 male Sprague–Dawley rats (5 months of age) were either exposed to 900 MHz CW (average power density $1 \pm 0.4\,\mathrm{mW/cm^2}$) or not (control group). Rats exposed 30 min/day, for 5 days/week for 4 weeks. The authors also did not observe significantly different values of weight of testes, testicular biopsy score count and the percentage of interstitial tissue. However, the mean height of the germinal epithelium was found decreased in the group of rats that had been irradiated.

Forgács et al. [43] repeatedly exposed male NMRI mice to 1800 MHz GSM like microwave radiation at 0.018–0.023 W/kg whole body SAR. 11–12 sham exposed and 11–12 exposed mice were used. The animals were exposed ten times (over 2 weeks) and the duration of exposure was 2 h/day. No microwave exposure-related morphological alterations were found in testis, epididymis and prostate.

Adult male rats were examined after exposure at subcrhronic exposure to RF emitted from a conventional cell phone on their testicular function. Sixteen Wistar rats were used at age 30 days. The animals were exposed for 1 h daily during 11 weeks. The experimental group ($n = 8$) was exposed to 1835–1850 MHz at 0.04–1.4 $\mathrm{mW/cm^2}$. Total body weight and absolute and relative testicular and epididymal weights did not change significantly. Epididymal sperm count was not significantly different between the groups. Regarding the histomorphological endpoints of the study, no difference was found between the experimental and control arm [44].

The effect of cellular phone emissions on sperm characteristics in 16 Sprague–Dawley rats were studied [45]. The laboratory animals were divided in two groups (experimental, control) and exposed to four cell phones which had a personal communications service code division multiple access frequency band of 1.9 GHz (800 MHz digital and 800 MHz analog). The rats received daily (3 h–30 min rest–3 h) cell phone exposure for 18 weeks. The SAR ranged from 0.9 to 1.80 W/kg whereas the power from 0.00001 to 0.607 W, according to the specific mode of function. The authors analyzed the morphology of the sperm cells from epididymis of rats. The percentage of deformities for the experimental group was 34.3% and the percentage of deformities for the control group was 32.1%. This difference in the occurrence of deformities between the two groups was not statistically significant ($p > .05$) through a paired t test. The total sperm counts from the testes were not significantly different between the two groups. None of the temperature differences between the two groups were statistically significant.

Sixteen Sprague–Dawley rats were used to evaluate the bcl-2 protein (an anti-apoptotic protein) in rat testes. The experimental group ($n = 8$) was exposed to commercial (GSM) cellular phones irradiation for 20 min/day for 1 month. Average power density was measured at 0.047 $\mathrm{mW/cm^2}$ and SAR levels changed between 0.29 and 0.87 W/kg. The testes were investigated by means of immunohistochemistry. No difference was observed between testes sections of the sham and experimental groups in terms of bcl-2 staining. These results indicate that the radiation emitted from 900 MHz cellular phones did not alter the anti-apoptotic protein in the testes of rats [46].

In order to investigate the apoptosis-inducing effect of mobile phone exposure on spermatogonia in seminiferous tubules, 31 Wistar albino male rats were divided in three groups such as cage control ($n = 10$), sham exposed ($n = 7$), and experimental ($n = 14$). The 2 h/day (7 days/week) exposure of 900 MHz radiation (power density 0.012–0.149 $\mathrm{mW/cm^2}$ and SAR 0.07–0.57 W/kg) over a period of 10 months was evaluated by means of immunohistochemistry. The long-term radiation did not affect the active caspace-3 levels in testes of rats. Caspace-3 is a typical feature of apoptosis [47].

4. Female genital system

Studies on the impact of RF in the female genital system are scarce. Two studies were conducted in order to evaluate the effects on endometrial apoptosis and the ameliorating effects of a combination of vitamin E and C against EMF damage.

Oral et al. [48], exposed sexually mature female rats (16 weeks old) to 900 MHz radiation, 30 min/day for 30 days. Twenty-four Wistar albino rats were divided in three groups (sham exposed, EMF exposed, EMF exposed treated with vitamin C and E). The animals were exposed at 1.04 $\mathrm{mW/cm^2}$ (SAR 0.016–4 W/kg). The effect of microwaves was examined in rat endometrium by means of immunohistochemistry. Endometrial apoptosis was observed. Guney et al. [49], repeated the experiment with the addition of another group (control). Histological changes in endometrium, diffuse and severe apoptosis in the endometrial surface, epithelial and glandular cells were reported regarding the group exposed to EMF. Also, eosinophilic leucocyte and lymphocyte infiltration were seen in the endometrial stroma.

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Table 2
Overview of investigations on EMF effects on animal development.

Animal species	Exposure frequency	Exposure parameters	Exposure duration	Endpoint	Results	Comments	Reference
Rat Sprague–Dawley	50 Hz	7, 70, 350 mT	22 h/day during 0–7 or 8–15 day of gestation	Effects on teratogenicity and embryonic development	No differences regarding embryonic deaths, fetal weight and teratogenicity		[50]
Mouse ICR	50 Hz	Sham (0.1–1 μT), 0.5, 5 mT	9 weeks♂ 2 weeks♀ prior to mating	Effects on teratogenicity and embryonic development	No differences regarding embryonic deaths, fetal weight and teratogenicity		[51]
Mouse Swiss Webster	0 Hz–25 MHz		1 week beginning from the 18th day of pregnancy	Morphological changes in brain, thymus, adrenal gland during embryonic development	Pathological changes were observed in the neonates		[52]
Rat Sprague–Dawley	60 Hz	0 (sham group), 5, 83.3, 500 mT.	22 h/day during 6–20 day of gestation	Developmental toxicity	No differences regarding embryonic deaths, fetal weight and teratogenicity		[53]
Chicken	50 Hz	1.33–7.32 mT	24 h	Effects on teratogenicity and embryonic development	Significant difference in the percentage of abnormal embryos versus control was found in 4.19, 5.32, 5.86, and 6.65 densities. Some embryos with extra ribs, defects in ribs and vertebrae, anuria and abnormal beaks were observed	Funding not mentioned	[54]
Mouse ICR	20 kHz	6.5 mT	8 h/day from 2.5 to 15.5 days post-coitum	Effects on teratogenicity and embryonic development	No statistically significant differences in the number of implantation, embryonic death, resorption, growth retarded fetuses, external and skeletal abnormalities		[55]
Chicken Leghorn HR7	50 Hz	1 μT, 500 μT, 1 mT	Continuous for 15 or 21 days	Effects on embryo/fetus	At 15 days of incubation body weight was significantly lower versus controls. At 21 days of incubation the body weight and cranial diameters were smaller versus control. No differences in brain weight were observed in all groups	Funding not mentioned	[56]
Mouse ♀	Static magnetic field	400 mT	6 min/day from 7.5 to 14.5 day of pregnancy	Teratogenic effects	Polydactylism, abdominal fissure, fused ribs, vestigial 13th rib, brain hernia, curled tail		[57]
Mouse ♀	50 Hz	1.2 mT	8 h/day during pregnancy	Body weight of dams, development of offspring	Fetal loss, malformed fetuses, retardation of growth of the offspring in the first 2 weeks after birth	Article in chinese	[58]
Chicken White Leghorn eggs	50 Hz	1.33–7.32 mT	4 days	Morphological evaluation of embryos/fetuses	Abnormal brain cavities, spina bifida, monophthalmia, ocular defects and growth retardation		[59]

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5. Developmental effects

The critical phases in the dynamic process of development take place mainly *in utero* (mammals) or *in ovo* (birds) i.e. during the embryonic period. The main bulk of investigations were performed regarding the possible effects on animals after irradiation, during *in utero* or *in ovo* development. The effects on development are determined by endpoints such as weight gain, congenital malformations, resorptions, and number of litters. These endpoints will be considered for various exposure conditions.The effects of EMF (mainly LF) on animal development are summarized in Table 2. Egg production was reduced (8%) when young laying hens have been continuously exposed to CW 915 MHz with an incident power of 800 mW during the first 2.5 weeks, 0 mW during the following week and 200 mW for the rest of experiment. Hatching of fertile and total eggs was not significantly influenced. No macroscopic malformations were observed in the chicks or dead embryos [60].

Jensh et al. [61] irradiated pregnant Wistar albino rats at a power density level of 10 mW/cm^2, at a frequency of 915 MHz and average SAR 3.57 W/kg. The animals were exposed for 6 h/day from day 1 to day 21 of gestation. No significant teratogenic signs were observed regarding the resorption rate, malformation rate, mean litter size, fetal weight and number of live and dead fetuses. The experiment was repeated and extended in order to analyze the embryonic and postnatal development of offspring [62]. Eleven pregnant rats were irradiated and 19 rats were used as control animals. All animals delivered and raised their offspring (F_{1a}) until weaning at 30 days of age. Ten days later females were rebred and teratologic evaluation was conducted on the resultant F_{1b} fetuses. At 90 days of age, reproductive capability was evaluated and a standard teratologic analysis performed on the resultant F_2 offspring. No significant morphologic changes were revealed.

Pregnant rats were exposed at 970 MHz for 22 h/day from the 1st to 19th day of pregnancy [63]. The SAR values varied from 0.07, 2.4 and 4.8 W/kg. The embryo mortality, fetal weight, skeletal ossification, as well as maternal fertility were evaluated. The exposure with SAR 4.8 W/kg caused reduced (−12%) fetal body weight versus the control. All the other examined parameters were not significantly different.

Klug et al. [64] exposed rat embryos (9.5 days old) for up to 36 h to 900 MHz. The modulation frequency was fixed at 215 Hz and the SAR values were calculated at 0.2, 1 and 5 W/kg. The endpoints of the experiment were crown-rump length, number of somites as well as embryonic malformations. No significant changes were observed on the growth and differentiation parameters of the embryos. Magras and Xenos [65] investigated the possible effects of radiofrequency radiation on prenatal development in mice. The study consisted of *in vivo* experiments at several places around an "antenna park" where the frequency emissions ranged from 88.5 to 950 MHz. At these locations RF power densities between 168 and 1053 nW/cm^2 were measured. Twelve pairs of mice, divided in two groups, were placed in locations of different power densities and were repeatedly mated five times. One hundred eighteen newborns were collected. They were measured, weighed, and examined macro- and microscopically. A progressive decrease in the number of newborns per dam was observed, which ended in irreversible infertility. The prenatal development of the newborns, however, evaluated by the crown-rump length, the body weight, and the number of the lumbar, sacral, and coccygeal vertebrae, was improved. Wistar albino rats [15] were exposed through pregnancy for 6 h each day to CW 915 MHz radiation at a power density level of 10 mW/cm^2. Teratologic evaluation included the following parameters: mean litter size, maternal organ weight and organ weight/body weight ratios, body weight ratios of various organs (brain, liver, kidneys, and ovaries), number of resorptions and resorption rate, number of abnormalities and abnormality rate, mean term fetal weight. Mothers were rebred, and the second, unexposed litters were evaluated for teratogenic effects. Animals exposed to 915 MHz did not exhibit any consistent significant alterations in any of the above parameters.

Wistar rats were continuously exposed [66] during pregnancy to a low-level (0.1 mW/cm^2) 900 MHz, 217 Hz pulse modulated EMF. Whole body average SAR values for the freely roaming, pregnant animals were measured in models; they ranged between 17.5 and 75 mW/kg. No differences between exposed and sham exposed dams or offspring were recorded in terms of litter size, evolution of body mass and developmental landmarks of litter mates. The effects of microwaves emitted by cellular phones on birth weights of rats were investigated by Dasdag et al. [67]. Thirty-six Wistar albino rats were divided into four groups. Each experimental or sham exposed group comprised six males or 12 females. The rats were exposed at 890–915 MHz (SAR 0.155 W/kg). Males were exposed daily for 3 × 1 min during 2 h/day for 1 month. Females were exposed in the same way until they gave birth. When the offspring became adult the experiment was repeated on them. No significant differences were observed between rectal temperatures in the sham and experimental groups. The birth weight of offspring in the experimental group was significantly lower than in the sham exposed group. However in the next generation of rats all parameters investigated were normal. Pregnant Sprague–Dawley rats were exposed [68] to ultra wide band (UWB) 0.1–1 GHz radiation in order to determine if teratological changes occur in rat pups as a result of (1) daily UWB exposures during gestation days 3 ± 18, or (2) as a result of both prenatal and postnatal (10 days) exposures. Dams were exposed either to (I) UWB irradiation with average whole body specific absorption rate 45 mW/kg (II) sham irradiation or (III) a positive control. Offspring were examined regarding litter size, sex-ratios, weights, coat appearance, and tooth eruption. The pups postnatally exposed were examined for hippocampal morphology. Generally, no significant differences were found between the exposed and sham group. The medial-to-lateral length of the hippocampus was significantly longer in the

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Table 3
Summary of animal studies on effects of EMF (related to mobile telephony), on reproduction and development.

Animal species	Exposure frequency	Endpoint	Effect	Reference
Chicken	915 MHz	Development	No	[60]
Rat	915 MHz	Development	No	[61]
Rat	915 MHz	Development	No	[62]
Rat	970 MHz	Development	No	[63]
Rat	915 MHz	Development	No	[15]
Rat	900 MHz	Development	No	[64]
Mouse	88.5–950 MHz	Fertility/development	Yes/no	[65]
Rat	890–915 MHz	Testes	Yes	[39]
Rat	900 MHz	Development	No	[66]
Rat	0.1–1 GHz	Development	No	[68]
Rat	890–915 MHz	Development	Yes	[67]
Chicken	900 MHz	Development	Yes	[69]
Rat	890–915 MHz	Testes	No	[40]
Chicken		Development	Yes	[70]
Rat	900 MHz	Testes	No	[42]
Mouse	900 MHz	Testes	No	[41]
White stork	900–1800 MHz phone mast	Reproduction	Yes	[74]
Chicken	900 MHz	Kidney development	Yes	[71]
Mouse	1800 MHz	Testes	No	[43]
Rat	900 MHz	Endometrium	Yes	[48]
Rat	900 MHz	Brain development	No	[72]
Rat	1835–1850 MHz	Testes	No	[44]
Rat	1.9 GHz	Sperm	No	[45]
Tit	1200–3000 MHz	Reproduction	No	[75]
Rat	900 MHz	Endometrium	Yes	[49]
Chicken	900 MHz	Development	Yes	[73]
Rat	900 MHz	Testes	No	[46]
Rat	900 MHz	Testes	No	[47]

UWB-exposed pups than in the sham exposed animals but could not correlated with neurological dysfunction. The male offspring exposed *in utero* to UWB mated significantly less frequently than sham exposed males, but when they did mate there was no difference in fertilization and offspring numbers from the sham group.

Bastide et al. [69] reported chicken embryo mortality from day 7 to day 11 of incubation. This mortality reached 64% compared to 11% in controls. The maximum level of embryonic mortality was observed in the eggs placed near the telephone.

Chicken embryos were exposed to EMF from GSM mobile phone during the embryonic development [70]. The embryo mortality rate in the incubation period increased to 75% versus 16% in control group.

Ingole and Ghosh [71] studied by means of light microscopy the developmental effects on the avian kidney of radiation, from a cell phone handset (900 MHz frequency, power of 2 W and SAR of 0.37 W/kg). The authors reported morphological alterations on the epithelium of the renal tubules as well as of the renal corpuscles in E6, E8 and E10 chicken embryos.

The possible impact of cell phone radiation in the developing central nervous system of male Wistar rats was examined [72]. The animals were exposed to 900 MHz signal for 2 h/day on 5 days/week. After 5 weeks of exposure at whole body average SAR of 0.3 or 3 W/kg or sham exposure no degenerative morphological changes were found.

The results about the effects of exposing fertilized chicken eggs to a mobile phone over the entire period of incubation were published recently [73]. In this study, a series of 4 incubations were employed. During each incubation, 4 groups were used (control I, control II, experimental, sham). In the experimental group, the cell phone in call position was placed near ($\leq$25 cm) the eggs, whereas in the sham group the cell phone in off position was placed 1.5 m away from the exposed group. A significantly higher percentage of embryo mortality was observed in the experimental compared to the sham group in 2 of the 4 incubations. The lethal effects of embryo development in the experimental group were mainly observed between the 9th and 12th day of incubation.

Another issue that in recent years has attracted the attention of scientists is the effects of radiation from RF antennas on the biology of wild birds.

Balmori [74] investigated the possible effects of EMF from phone masts on a population of White stork (*Ciconia ciconia*). The total productivity in the nests located within 200 m of antennas was 0.86 ± 0.16 versus 1.6 ± 0.14 for those located further than 300 m. Another interesting observation, was that, 40% of the nests within 200 m of the antennae never had any chicks, while only 3.3% located further than 300 m never had chicks.

The influence of a military radar station [75] emitting pulsed modulated microwave radiation of 1200–3000 MHz was examined in tits (*Parus* sp). Experimental nest-boxes

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were either exposed to a mean level of 3.41 ± 1.38 or $1.12 \pm 0.84\,W/m^2$. For control nest-boxes the exposure ranged from 0.001 to 0.01 W/m^2. No statistically significant differences in the number of eggs or in the number of nestlings were observed between the two series (exposed, control) of tits.

6. Conclusions

The EMF were, are and will be a part of our life. The progress of science will provide the world with new EMF emitting technologies and subsequently with new problems. The monitoring of literature on this scientific field shows a shift of research which follows exactly the new technologies. The era of mobile telephony is beginning.

The evaluation of the possible effects of EMF on the living organism is a complex process that needs the combined contributions of many scientific disciplines. Due to the need for expertise in many different sciences, together with the technical problems of radiation studies, many times the published results are considered deficient in certain aspects. This is inevitable, and not an indication of poor quality. The inability to observe a biological effect in a particular study does not necessarily mean that such effect or/and adverse health effect is not present.

The vertebrate animal studies summarized in the present paper do not suggest strong effects of LF EMF on the male genital system. However, some studies on the development of animals, showed sensitivity, mainly observed in chickens. There is no convincing evidence from studies of mammals (Table 3), that exposure to EMF at levels associated with mobile telecommunications could be harmful for embryonic or postnatal development or for male fertility. On the other hand, the birds appeared to be more sensitive. The effects of EMF on the female genital system need further attention, since two experimental studies cannot lead to definitive conclusions.

The positive findings of the experimental studies with vertebrate animals are mainly attributed to the thermal effects of EMF. No valid evidence was found for the occurrence of non-thermal effects. However the non-thermal mechanisms must be the next target of the research.

The majority of reviewed studies were conducted in laboratories. This fact cannot represent the realistic situation of cell phone communication. On the other hand, the *in vivo* and simultaneously *in situ* studies are very scarce. Only Magras and Xenos conducted an *in situ* experiment which took place near an antenna park. That is because this kind of experiment is very difficult to carry out, and interaction with other exogenous factors could change the results.

One particular deficiency in most studies is that they describe experiments with acute or short-term exposure of animals on EMF. Experiments are needed to perform long-term exposure in order to demonstrate the chronic impact of EMF.

Another point that must be elucidated is that the majority of experimental animals used were small rodents (mice and rats), as well as chicken embryos. Further research is needed with the use of bigger animals such as dog and sheep.

The radiations emitted from masts that are situated in many rural and sylvatic areas could be possibly pathogenic in the wild animals. The wild animal populations could be candidate "experimental material" for closer observation of the possible effects of EMF on vertebrate models.

An important and intriguing aspect of the research is the possible role of the combination of RF with other pollutants such as chemical substances and other forms of radiation, as well as the interaction with drugs.

The potential health effects of EMF should be continually reassessed as new research results become available. EMF exposure guidelines also need to be updated or reconsidered as new scientific information on radiation and health risks is produced. However, additional studies might increase our understanding of the sensitivity of organisms to EMF.

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Electromagnetic pollution from phone masts. Effects on wildlife

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Abstract

A review on the impact of radiofrequency radiation from wireless telecommunications on wildlife is presented. Electromagnetic radiation is a form of environmental pollution which may hurt wildlife. Phone masts located in their living areas are irradiating continuously some species that could suffer long-term effects, like reduction of their natural defenses, deterioration of their health, problems in reproduction and reduction of their useful territory through habitat deterioration. Electromagnetic radiation can exert an aversive behavioral response in rats, bats and birds such as sparrows. Therefore microwave and radiofrequency pollution constitutes a potential cause for the decline of animal populations and deterioration of health of plants living near phone masts. To measure these effects urgent specific studies are necessary.
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Keywords: Effects on wildlife; Effects on birds; Electromagnetic radiation; Mammals; Microwaves; Mobile telecommunications; Non-thermal effects; Phone masts; Radiofrequencies

1. Introduction

Life has evolved under the influence of two omnipresent forces: gravity and electromagnetism. It should be expected that both play important roles in the functional activities of organisms [1]. Before the 1990's radiofrequencies were mainly from a few radio and television transmitters, located in remote areas and/or very high places. Since the introduction of wireless telecommunication in the 1990's the rollout of phone networks has caused a massive increase in electromagnetic pollution in cities and the countryside [2,3].

Multiple sources of mobile communication result in chronic exposure of a significant part of the wildlife (and man) to microwaves at non-thermal levels [4]. In recent years, wildlife has been chronically exposed to microwaves and RFR (Radiofrequency radiation) signals from various sources, including GSM and UMTS/3G wireless phones and base stations, WLAN (Wireless Local Area Networks), WPAN (Wireless Personal Area Networks such as Bluetooth), and DECT (Digital Enhanced (former European) Cordless Telecommunications) that are erected indiscriminately without studies of environmental impact measuring long-term effects. These exposures are characterized by low intensities, varieties of signals, and long-term durations. The greater portion of this exposure is from mobile telecommunications (geometric mean in Vienna: 73% [5]). In Germany the GSM cellular phone tower radiation is the dominating high frequency source in residential areas [6]. Also GSM is the dominating high frequency source in the wilderness of Spain (personal observation).

Numerous experimental data have provided strong evidence of athermal microwave effects and have also indicated several regularities in these effects: dependence of frequency within specific frequency windows of "resonance-type"; dependence on modulation and polarization; dependence on intensity within specific intensity windows, including super-low power density comparable with intensities from base stations/masts [4,7–9]. Some studies have demonstrated different microwave effects depending on wavelength in the range of mm, cm or m [10,11]. Duration of exposure may be as important as power density. Biological effects resulting from electromagnetic field radiation might depend on dose, which indicates long-term accumulative effects [3,9,12]. Modulated and pulsed radiofrequencies seem to be more effective in producing effects [4,9]. Pulsed waves (in blasts), as well as certain low frequency modulations exert greater

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biological activity [11,13–15]. This observation is important because cell phone radiation is pulsed microwave radiation modulated at low frequencies [8,9].

Most of the attention on possible biological effects of electromagnetic radiation from phone masts has been focused on human health [5,16–21]. The effects of electromagnetic pollution on wildlife, have scarcely been studied [22–25].

The objective of this review is to detail advances in knowledge of radiofrequencies and microwave effects on wildlife. Future research may help provide a better understanding of electromagnetic field (EMF) effects on wildlife and plants and their conservation.

2. Effects on exposed wildlife

2.1. Effects on birds

2.1.1. Effects of phone mast microwaves on white stork

In monitoring a white stork (*Ciconia ciconia*) population in Valladolid (Spain) in vicinity of Cellular Phone Base Stations, the total productivity in nests located within 200 m of antennae, was 0.86 ± 0.16. For those located further than 300 m, the result was practically doubled, with an average of 1.6 ± 0.14. Very significant differences among total productivity were found ($U = 240$; $P = 0.001$, Mann–Whitney test). Twelve nests (40%) located within 200 m of antennae never had chicks, while only one (3.3%) located further than 300 m had no chicks. The electric field intensity was higher on nests within 200 m (2.36 ± 0.82 V/m) than nests further than 300 m (0.53 ± 0.82 V/m). In nesting sites located within 100 m of one or several cellsite antennae with the main beam of radiation impacting directly (Electric field intensity >2 V/m) many young died from unknown causes. Couples frequently fought over nest construction sticks and failed to advance the construction of the nests. Some nests were never completed and the storks remained passively in front of cellsite antennae. These results indicate the possibility that microwaves are interfering with the reproduction of white stork [23]. (Fig. 1)

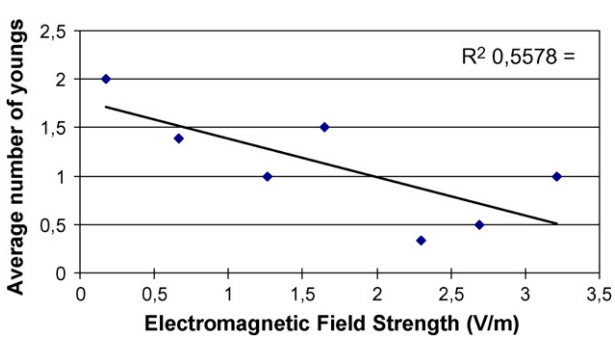

Fig. 1. Average number of youngs and electric field intensity (V/m) in 60 nests of white storks (*Ciconia ciconia*) (Hallberg, Ö with data of Balmori, 2005 [23]).

2.1.2. Effects of phone mast microwaves on house sparrows

A possible effect of long-term exposure to low-intensity electromagnetic radiation from mobile phone (GSM) base stations on the number of house sparrows during the breeding season was studied in Belgium. The study was carried out sampling 150 point locations within six areas to examine small-scale geographic variation in the number of house sparrow males and the strength of electromagnetic radiation from base stations. Spatial variation in the number of house sparrow males was negative and highly significantly related to the strength of electric fields from both the 900 and 1800 MHz downlink frequency bands and from the sum of these bands (Chi-square-tests and AIC-criteria, $P < 0.001$). This negative relationship was highly similar within each of the six study areas, despite differences among areas in both the number of birds and radiation levels. Fewer house sparrow males were seen at locations with relatively high electric field strength values of GSM base stations and therefore support the notion that long-term exposure to higher levels of radiation negatively affects the abundance or behavior of house sparrows in the wild [24].

In another study with point transect sampling performed at 30 points visited 40 times in Valladolid (Spain) between 2002 and 2006, counting the sparrows and measuring the mean electric field strength (radiofrequencies and microwaves: 1 MHz to 3 GHz range). Significant declines ($P = 0.0037$) were observed in mean bird density over time, and significantly low bird density was observed in areas with high electric field strength. The logarithmic regression of the mean bird density vs. field strength groups (considering field strength in 0.1 V/m increments) was $R = -0.87$; $P = 0.0001$ According to this calculation, no sparrows would be expected to be found in an area with field strength >4 V/m [25]. (Fig. 2)

In the United Kingdom a decline of several species of urban birds, especially sparrows, has recently happened [26]. The sparrow population in England has decreased in the last 30 years from 24 million to less than 14. The more abrupt decline, with 75% descent has taken place from 1994 to 2002. In 2002, the house sparrow was added to the Red List of U.K. endangered species [27]. This coincides with the rollout of mobile telephony and the

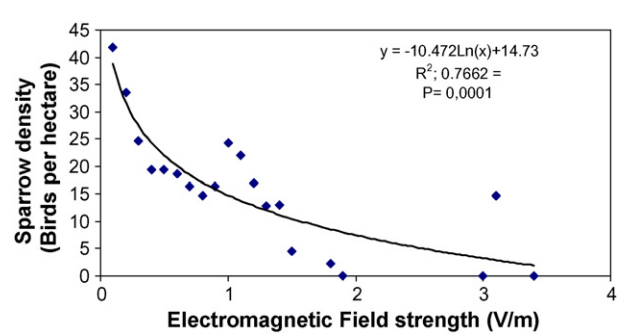

Fig. 2. Mean sparrow density as a function of electric field strength grouped in 0.1 V/m. (Balmori and Hallberg, 2007 [25]).

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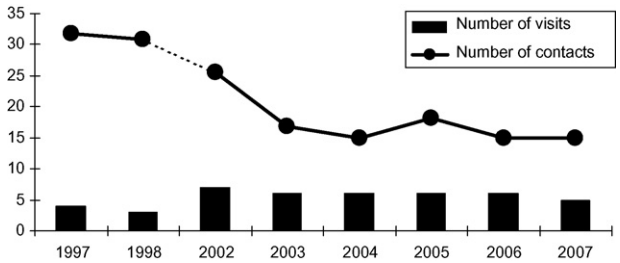

Fig. 3. Annual number of contacts (Mean) for 14 species studied in "Campo Grande" urban park (lack the information of the years 1999–2001).

possible relationship of both circumstances should be investigated.

In Brussels, many sparrows have disappeared recently [28]; similar declines have been reported in Dublin [29]. Van der Poel (cited in Ref. [27]) suggested that sparrows might be declining in Dutch urban centres also.

2.1.3. *Effects on the bird community at an urban park*

Microwaves may be affecting bird populations in places with high electromagnetic pollution. Since several antennas were installed in proximities of "Campo Grande" urban park (Valladolid, Spain) the bird population has decreased and a reduction of the species and breeding couples has occurred. Between 1997 and 2007, of 14 species, 3 species have disappeared, 4 are in decline and 7 stay stable (Balmori, unpublished data) (Fig. 3). In this time the air pollution (SO2, NO2, CO and Benzene) has diminished.

During the research some areas called "silence areas" contaminated with high microwave radiation (>2 V/m), where previously different couples usually bred and later disappeared, have been found. Several anomalies in magpies (*Pica pica*) were detected: plumage deterioration, locomotive problems (limps and deformations in the paws), partial albinism and melanism, especially in flanks [30]. Recently cities have increased cases of partial albinism and melanism in birds (*Passer domesticus*, *Turdus merula* and *P. pica*) (personal observation).

2.1.4. *Possible physiological mechanisms of the effects found in birds*

Current scientific evidence indicates that prolonged exposure to EMFs, at levels that can be encountered in the environment, may affect immune system function by affecting biological processes [3,31,32]. A stressed immune system may increase the susceptibility of a bird to infectious diseases, bacteria, viruses, and parasites [33].

The plumage of the birds exposed to microwaves looked, in general, discolorated and lack of shine. This not only occurred in ornamental birds; such as peacocks, but also in wild birds; such as, tits, great tits, house sparrows, etc (personal observation). We must mention that plumage deterioration is the first sign of weakening or illnesses in birds since damaged feathers are a sure sign of stress.

Physiological conditions during exposure minimize microwave effects. Radical scavengers/antioxidants might be involved in effects of microwaves [4].

Microwaves used in cellphones produce an athermal response in several types of neurons of the birds nervous system [34]. Several studies addressed behavior and teratology in young birds exposed to electromagnetic fields [23,25,35–37]. Most studies indicate that electromagnetic field exposure of birds generally changes, but not always consistently in effect or in direction, their behavior, reproductive success, growth and development, physiology and endocrinology, and oxidative stress [37]. These results can be explained by electromagnetic fields affecting the birds' response to the photoperiod as indicated by altered melatonin levels [38].

Prolonged mobile phone exposure may have negative effects on sperm motility characteristics and male fertility as has been demonstrated in many studies made in man and rats [39–46]. EMF and microwaves can affect reproductive success in birds [23,25,35,36,47]. EMF exposure affected reproductive success of kestrels (*Falco sparverius*), increasing fertility, egg size, embryonic development and fledging success but reducing hatching success [35,36].

The radiofrequency and microwaves from mobile telephony can cause genotoxic effects [48–55]. Increases in cytological abnormalities imply long-term detrimental effects since chromosomal damage is a mechanism relevant to causation of birth defects and cancer [55].

Long-term continuous, or daily repeated EMF exposure can induce cellular stress responses at non-thermal power levels that lead to an accumulation of DNA errors and to inhibition of cell apoptosis and cause increased permeability of blood–brain barrier due to stabilization of endothelial cell stress fibers. Repeated occurrence of these events over a long period of time (years) could become a health hazard due to a possible accumulation of brain tissue damage. These findings have important implications with regards to potential dangers from prolonged and repeated exposure to non-ionizing radiation [56,57].

Pulsed magnetic fields can have a significant influence on the development and incidence of abnormalities in chicken embryos. In five of six laboratories, exposed embryos exhibited more structural anomalies than controls. If the data from all six laboratories are pooled, the difference for the incidence of abnormalities in exposed embryos and controls is highly significant [58]. Malformations in the nervous system and heart, and delayed embryo growth are observed. The embryo is most sensitive to exposure in the first 24 h of incubation [58]. An increase in the mortality [59] and appearance of morphological abnormalities, especially of the neural tube [13,60,61] has been recorded in chicken embryos exposed to pulsed magnetic fields, with different susceptibility among individuals probably for genetic reasons. A statistically significant high mortality rate of chicken embryos subjected to radiation from a cellphone, compared to the control group exists [62,63]. In another study eggs exposed to a magnetic

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field intensity of 0.07 T showed embryonic mortality during their incubation was higher. The negative effect of the magnetic field was manifested also by a lower weight of the hatched chicken [64]. Bioelectric fields have long been suspected to play a causal role in embryonic development. Alteration of the electrical field may disrupt the chemical gradient and signals received by embryo cells. It appears that in some manner, cells sense their position in an electrical field and respond appropriately. The disruption of this field alters their response. Endogenous current patterns are often correlated with specific morphogenetic events [65].

Available data suggests dependencies of genotype, gender, physiological and individual factors on athermal microwave effects [4,9]. Genomic differences can influence cellular responses to GSM Microwaves. Data analysis has highlighted a wide inter-individual variability in response, which was replicated in further experiments [4]. It is possible that each species and each individual, show different susceptibility to radiation, since vulnerability depends on genetic tendency, and physiologic and neurological state of the irradiated organism [15,35–37,61,66–68]. Different susceptibility of each species has also been proven in wild birds exposed to electromagnetic fields from high-voltage power lines [47].

2.2. *Effects on mammals*

2.2.1. *Alarm and aversion behavior*

Rats spent more time in the halves of shuttle boxes that were shielded from 1.2 GHz. Microwaves irradiation. The average power density was about 0.6 mW/cm^2. Data revealed that rats avoided the pulsed energy, but not the continuous energy, and less than 0.4 mW/cm^2 average power density was needed to produce aversion [69]. Navakatikian & Tomashevskaya [70] described a complex series of experiments in which they observed disruption of rat behavior (active avoidance) from radiofrequency radiation. Behavioral disruption was observed at a power density as low as 0.1 mW/cm^2 (0.027 W/kg). Mice in an experimental group exposed to microwave radiation expressed visible individual panic reaction, disorientation and a greater degree of anxiety. In the sham exposed group these deviations of behavior were not seen and all animals show collective defense reaction [71]. Microwave radiation at 1.5 GHz pulsing 16 ms. At 0.3 mW/cm^2 power density, in sessions of 30 min/day over one month produced anxiety and alarm in rabbits [72].

Electromagnetic radiation can exert an aversive behavioral response in bats. Bat activity is significantly reduced in habitats exposed to an electromagnetic field strength greater than 2 V/m [73]. During a study in a free-tailed bat colony (*Tadarida teniotis*) the number of bats decreased when several phone masts were placed 80 m from the colony [74].

2.2.2. *Deterioration of health*

Animals exposed to electromagnetic fields can suffer a deterioration of health and changes in behavior [75,76].

There was proof of frequent death in domestic animals; such as, hamsters and guinea pigs, living near mobile telecommunication base stations (personal observation).

The mice in an experimental group exposed to microwave radiation showed less weight gain compared to control, after two months. The amount of food used was similar in both groups [71]. A link between electromagnetic field exposure and higher levels of oxidative stress appears to be a major contributor to aging, neurodegenerative diseases, immune system disorders, and cancer in mammals [33].

The effects from GSM base transceiver station (BTS) frequency of 945 MHz on oxidative stress in rats were investigated. When EMF at a power density of 3.67 W/m^2, below current exposure limits, were applied, MDA (malondialdehyde) level was found to increase and GSH (reduced glutathione) concentration was found to decrease significantly ($P < 0.0001$). Additionally, there was a less significant ($P = 0.0190$) increase in SOD (superoxide dismutase) activity under EM exposure [77].

2.2.3. *Problems in reproduction*

In the town of Casavieja (Ávila, Spain) a telephony antenna was installed that had been in operation for about 5 years. Then some farmers began blaming the antenna for miscarriages in many pigs, 50–100 m from the antenna (on the outskirts of the town). Finally the topic became so bad that the town council decided to disassemble the antenna. It was removed in the spring 2005. From this moment onwards the problems stopped (C. Lumbreras personal communication).

A Greek study reports a progressive drop in the number of rodent births exposed to radiofrequencies. The mice exposed to 0.168 μW/cm^2 become sterile after five generations, while those exposed to 1.053 μW/cm^2 became sterile after only three generations [22].

In pregnant rats exposed to 27.12 MHz continuous waves at 100 μW/cm^2 during different periods of pregnancy, half the pregnancies miscarried before the twentieth day of gestation, compared to only a 6% miscarriage rate in unexposed controls, and 38% of the viable foetuses had incomplete cranial ossification, compared to less than 6% of the controls. Findings included a considerable increase in the percentage of total reabsorptions (post-implantation losses consequent to RF radiation exposure in the first post-implantation stage). Reduced body weight in the exposed dams reflected a negative influence on their health. It seems that the irradiation time plays an important role in inducing specific effects consequent to radiofrequency radiation exposure [78]. There was also a change in the sex ratio, with more males born to rats that had been irradiated from the time of conception [2]. Moorhouse and Macdonald [79] find a substantial decline in female Water Vole numbers in the radio-collared population, apparently resulting from a male skew in the sex ratios of offspring born to this population. Recruits to the *radio-tracked* population were skewed heavily in favour of males (43:13). This suggests that radio-collaring of females caused male-skewed sex ratios.

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Mobile phone exposure may have negative effects on sperm motility characteristics and male fertility in rats [46]. Other studies find a decrease of fertility, increase of deaths after birth and dystrophic changes in their reproductive organs [11]. Intermittent exposure showed a stronger effect than continuous exposure [4]. Brief, intermittent exposure to low-frequency EM fields during the critical prenatal period for neurobehavioral sex differentiation can demasculinize male scent marking behavior and increase accessory sex organ weights in adulthood [80].

In humans, magnetic field exposures above 2.0 mG were positively associated with miscarriage risk [81]. Exposure of pregnant women to mobile phone significantly increased foetal and neonatal heart rate, and significantly decreased the cardiac output [82].

2.2.4. Nervous system

Microwaves may affect the blood brain barrier which lets toxic substances pass through from the blood to the brain [83]. Adang et al. [84] examined the effect of microwave exposure to a GSM-like frequency of 970 MHz pulsed waves on the memory in rats by means of an object recognition task. The rats that have been exposed for 2 months show normal exploratory behavior. The animals that have been exposed for 15 months show derogatory behavior. They do not make the distinction between a familiar and an unfamiliar object. In the area that received radiation directly from "Location Skrunda Radio Station" (Latvia), exposed children had less developed memory and attention, their reaction time was slower and neuromuscular apparatus endurance was decreased [85]. Exposure to cell phones prenatally and, to a lesser degree, postnatally was associated with behavioral difficulties such as emotional and hyperactivity problems around 7 years of age [86]. Electromagnetic radiation caused modification of sleep and alteration of cerebral electric response (EEG) [87–89]. Microwave radiation from phone masts may cause aggressiveness in people and animals (personal observation).

2.3. Effects on amphibians

Disappearance of amphibians and other organisms is part of the global biodiversity crisis. An associated phenomenon is the appearance of large numbers of deformed amphibians. The problem has become more prevalent, with deformity rates up to 25% in some populations, which is significantly higher than previous decades [90]. Balmori [91] proposed that electromagnetic pollution (in the microwave and radiofrequency range) is a possible cause for deformations and decline of some wild amphibian populations.

Two species of amphibians were exposed to magnetic fields at various stages of development. A brief treatment of early amphibian embryos produced several types of abnormalities [92]. Exposure to a pulsed electromagnetic field produced abnormal limb regeneration in adult Newts [93]. Frog tadpoles (*Rana temporaria*) developed under electromagnetic field (50 Hz, 260 A/m) have increased mortality. Exposed tadpoles developed more slowly and less synchronously than control tadpoles and remain at the early stages for longer. Tadpoles developed allergies and EMF caused changes in blood counts [94].

In a current study exposing eggs and tadpoles ($n = 70$) of common frog (*R. temporaria*) for two months, from the phase of eggs until an advanced phase of tadpole, to four telephone base stations located 140 m away: with GSM system 948.0–959.8 MHz; DCS system: 1830.2–1854.8; 1855.2–1879.8 MHz. and UMTS system: 1905–1910; 1950–1965; 2140–2155 MHz. (electric field intensity: 1.847–2.254 V/m). A low coordination of movements, an asynchronous growth, with big and small tadpoles, and a high mortality (90%) was observed. The control group ($n = 70$), under the same conditions but inside a Faraday cage (metallic shielding component: EMC-reinforcement fabrics 97442 Marburg Technic), the coordination of movements was normal, the development was synchronously and the mortality rate was only 4.2% [95].

2.4. Effects on insects

The microwaves may affect the insects. Insects are the basis and key species of ecosystems and they are especially sensitive to electromagnetic radiation that poses a threat to nature [96].

Carpenter and Livstone [97] irradiated pupae of Tenebrio molitor with 10 GHz microwaves at 80 mW for 20–30 min and 20 mW for 120 min obtained a rise in the proportion of insects with abnormalities or dead. In another study exposing fruit flies (*Drosophila melanogaster*) to mobile phone radiation, elevated stress protein levels (Hsp70) was obtained, which usually means that cells are exposed to adverse environmental conditions ('non-thermal shock') [98]. Panagopoulos et al. [99] exposed fruit flies (*D. melanogaster*) to radiation from a mobile phone (900 MHz) during the 2–5 first days of adulthood. The reproductive capacity of the species reduced by 50–60% in modulated radiation conditions (emission while talking on the phone) and 15–20% with radiation nomodulated (with the phone silent). The results of this study indicate that this radiation affects the gonadal development of insects in an athermal way. The authors concluded that radio frequencies, specifically GSM, are highly bioactive and provoke significant changes in physiological functions of living organisms. Panagopoulos et al. [100] compare the biological activity between the two systems GSM 900 MHz and DCS 1800 MHz in the reproductive capacity of fruit flies. Both types of radiation were found to decrease significantly and non-thermally the insect's reproductive capacity, but GSM 900 MHz seems to be even more bioactive than DCS 1800 MHz. The difference seems to be dependent mostly on field intensity and less on carrier frequency.

A study in South Africa finds a strong correlation between decrease in ant and beetle diversity with the

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electromagnetic radiation exposure (D. MacFadyen, personal communication.). A decrease of insects and arachnids near base stations was detected and corroborated by engineers and antenna's maintenance staff [101]. In houses near antennas an absence of flies, even in summer, was found.

In a recent study carried out with bees in Germany, only a few bees irradiated with DECT radiation returned to the beehive and they needed more time. The honeycomb weight was lower in irradiated bees [102]. In recent years a "colony collapse disorder" is occurring that some authors relate with pesticides and with increasing electromagnetic pollution [96].

The disappearance of insects could have an influence on bird's weakening caused by a lack of food, especially at the first stages in a young bird's life.

2.5. *Effects on trees and plants*

The microwaves may affect vegetables. In the area that received radiation directly from "Location Skrunda Radio Station" (Latvia), pines (*Pinus sylvestris*) experienced a lower growth radio. This did not occur beyond the area of impact of electromagnetic waves. A statistically significant negative correlation between increase tree growth and intensity of electromagnetic field was found, and was confirmed that the beginning of this growth decline coincided in time with the start of radar emissions. Authors evaluated other possible environmental factors which might have intervened, but none had noticeable effects [103]. In another study investigating cell ultrastructure of pine needles irradiated by the same radar, there was an increase of resin production, and was interpreted as an effect of stress caused by radiation, which would explain the aging and declining growth and viability of trees subjected to pulsed microwaves. They also found a low germination of seeds of pine trees more exposed [104]. The effects of Latvian radar was also felt by aquatic plants. *Spirodela polyrrhiza* exposed to a power density between 0.1 and 1.8 μW/cm^2 had lower longevity, problems in reproduction and morphological and developmental abnormalities compared with a control group who grew up far from the radar [105].

Chlorophylls were quantitatively studied in leaves of black locust (*Robinia pseudoacacia* L.) seedlings exposed to high frequency electromagnetic fields of 400 MHz. It was revealed that the ratio of the two main types of chlorophyll was decreasing logarithmically to the increase of daily exposure time [106].

Exposed tomato plants (*Lycopersicon esculentum*) to low level (900 MHz, 5 V/m) electromagnetic fields for a short period (10 min) measured changes in abundance of three specific mRNA after exposure, strongly suggesting that they are the direct consequence of application of radio-frequency fields and their similarities to wound responses suggests that this radiation is perceived by plants as an injurious stimulus [107]. Non-thermal exposure to radiofrequency fields induced oxidative stress in duckweed (*Lemna minor*) as well as unespecific stress responses, especially of antioxidative enzymes [108].

For some years progressive deterioration of trees near phone masts have been observed in Valladolid (Spain). Trees located inside the main lobe (beam), look sad and feeble, possibly slow growth and a high susceptibility to illnesses and plagues. In places we have measured higher electric field intensity levels of radiation (>2 V/m) the trees show a more notable deterioration [109]. The tops of trees are dried up where the main beams are directed to, and they seem to be most vulnerable if they have their roots close to water. The trees don't grow above the height of the other ones and, those that stand out far above, have dried tops (Hargreaves, personal communication and personal observation). White and black poplars (*Populus sp*.) and willows (*Salix sp*.) are more sensitive. There may be a special sensitivity of this family exists or it could be due to their ecological characteristics forcing them to live near water, and thus electric conductivity. Other species as *Platanus sp*. and *Lygustrum japonicum,* are more resistant (personal observation). Schorpp [110] presents abundant pictures and explanations of what happens to irradiated trees.

3. Conclusions

This literature review shows that pulsed telephony microwave radiation can produce effects especially on nervous, cardiovascular, immune and reproductive systems [111]:

- Damage to the nervous system by altering electroencephalogram, changes in neural response or changes of the blood–brain barrier.
- Disruption of circadian rhythms (sleep–wake) by interfering with the pineal gland and hormonal imbalances.
- Changes in heart rate and blood pressure.
- Impairment of health and immunity towards pathogens, weakness, exhaustion, deterioration of plumage and growth problems.
- Problems in building the nest or impaired fertility, number of eggs, embryonic development, hatching percentage and survival of chickens.
- Genetic and developmental problems: problems of locomotion, partial albinism and melanism or promotion of tumors.

In the light of current knowledge there is enough evidence of serious effects from this technology to wildlife. For this reason precautionary measures should be developed, alongside environmental impact assessments prior to installation, and a ban on installation of phone masts in protected natural areas and in places where endangered species are present. Surveys should take place to objectively assess the severity of effects.

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FM-radio and TV tower signals can cause spontaneous hand movements near moving RF reflector

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Abstract

For testing human sensitivity to radio frequency (RF) standing waves a movable reflecting wall was constructed. Radio waves from the radio–TV tower reflected back and formed a standing wave near the reflector. When the reflector was moved, the position of the maximums of the standing waves changed and the electromagnetic intensity changed in the body of the standing test subject. The computer with an AD-converter registered the signals of the hand movement transducer and the RF-meter with 100 MHz dipole antennas. A total of 29 adults of different ages were tested. There were 9 persons whose hand movement graphs included features like the RF-meter. Six showed responses that did not correlate with the RF-meter. There were also 14 persons who did not react at all. Sensitive persons seem to react to crossing standing waves of the FM-radio or TV broadcasting signals.
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Keywords: Sensorimotor responses; Radio frequency standing waves

1. Introduction

Radio frequency radiation (RFR) has been studied intensively in the near GHz region. Subjective symptoms, sleeping problems and cognitive performance have been reported in subjects living near mobile phone base stations [1]. In the recent past, frequencies of FM-radio and television (TV) signals have been much less studied even though these frequencies cause biological and health effects, too. The whole body resonance frequency of an average man and thus the maximum absorption of RF energy occur at 70–80 MHz [2]. This is near the frequencies used in very high frequency (VHF) broadcasting. The head and limbs absorb much more energy than the torso at frequencies above body resonance [3]. Greatest absorption in the head region of man occurs at a frequency of about 375 MHz [4]. Absorption is stronger for wave propagation from head to toe than it is when the electric field is parallel to the long axis. The authors [4] believed that the enchanced absorption in the head region may make head resonance significant in the study of behavioral effects, blood–brain barrier permeability, cataractogenesis, and other microwave bioeffects. Even increased health risks like cancer, especially melanoma incidence, near FM broadcasting and television transmitters have been reported [5,6].

Nerve impulses initiate muscle contraction by calcium ion release from the sarcoplasmic reticulum, which takes place when electric nerve signals reach the plasma membrane and T-tubules of muscle fibers [7]. Voltage dependent Ca-channels open. Acetylcholine esterase (AChE) breaks down the acetylcholine, and Na-channels close [7]. It has been reported that the number of Ca^{2+} ions liberated from hen's frontal brain depends on the modulation frequency of the weak VHF radiation, with a maximum at a frequency of 16 Hz, while an unmodulated field causes no ion release [2,8]. Multiple RF power-density windows in calcium ion release from brain tissue have presented [9]. A significant decrease in AChE activity has been found in rats exposed to radio frequency radiation of 147 MHz and its sub-harmonics 73.5 and 36.75 MHz amplitude modulated at 16 and 76 Hz. A decrease in AChE activity was independent of carrier wave frequencies [10].

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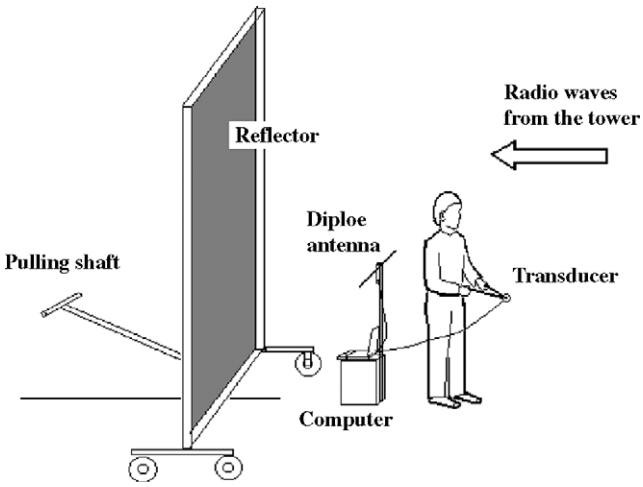

Fig. 1. Testing human radio wave sensitivity. Radio waves from the TV tower reflect back from the reflector and form a standing wave. When the reflector moves, the position of the maximums of the standing wave change, and the electromagnetic intensity changes in the body of the test subject. The computer with an AD-converter registers the signals of hand movement transducer and the RF-meter with the dipole antennas.

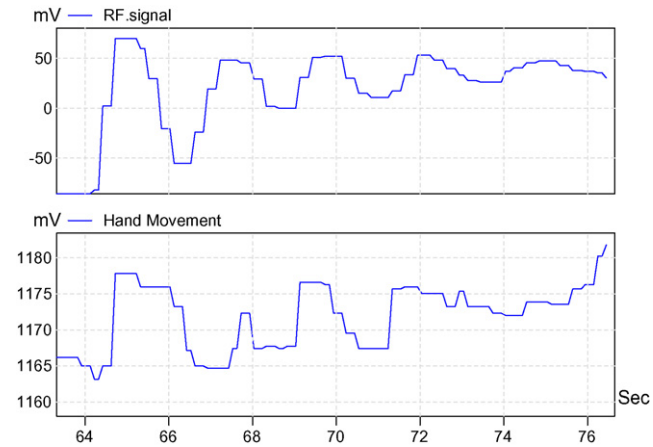

Fig. 2. Hand movements near the moving RF reflector. The standing waves moved slowly with the reflector. Intensity of the electric field was measured with the broadband RF-meter with horizontal dipole antennas. Variation of the field intensity is presented in the upper curve and the hand movements of the standing test person are in the lower curve.

As there is previous evidence from human and animal studies that electromagnetic irradiation has effects in the brain, the aim of the present study was to find out, if the motor responses are generated in sensitive persons, when they move across a set of standing waves caused by radiation of a FM-radio and TV tower. The connection between the hand movements and the integrated intensity of electromagnetic field of FM-radio broadcasting were recorded.

2. Methods

The wavelength of a 100-MHz radio wave is 3 m. For testing human sensitivity to moving standing waves a movable reflecting wall with wooden frame 3 m height and 5 m wide was constructed (Fig. 1). Steel net of 20 mm × 20 mm mesh was used. Five horizontal net slices of 60 cm wide were bound together with steel wire forming a radio waves reflecting surface. The test place was 5 km from the FM-radio tower. The frame was placed in an open field perpendicular to the incoming wave. The test subject was standing back towards the frame, and he had the hand movement transducer in his hands. The RF-meter with horizontal dipole antenna was close behind him. When started, the frame was 2 m from his back and it was moved 20 m forth and back. The computer registered both signals. The method and the aim of the test were at first presented, in brief, to the test persons. All together 29 adult persons of different ages were tested. They were participants in a seminar relating to effects of electric fields, and thus they possibly do not represent a normal population.

The broadband (30–300 MHz) RF-meter and the hand movement transducer were constructed for this study by the authors. The signals were digitised by Pico high resolution data logger (ADC16). The radio frequency spectrum was measured using a spectrum analyser (GW instek GSP-827, 2.7 GHz) with 1.5 m horizontal dipole antennas. When measured, the antenna was fastened to a wooden frame 1 m from the ground.

3. Results and discussion

Results on the movable frame showed different hand movement reactions of the test subjects. There were 9 persons who reacted like the RF-meter (Fig. 2), 6 persons whose graphs, though obvious, showed no correlation to the RF-meter and 14 persons who did not react or showed only small noise like changes in their graphs (Table 1). Spectrum at the test place contains mainly the FM-radio broadcasting signals and four digital TV signals (Fig. 3). Most prominent (85 dB μV, approximately 50 mV/m) are the 6 horizontally polarized FM-radio signals (Fig. 4).

Resonances in body parts affects the power absorption. Theoretically, the optimal length of a thin antenna in radio-frequency reception is nearly half of the wavelength of the

Table 1
Reactions to standing waves of FM-radio signals. Classification of results of 29 tested persons. Test subject was standing and the radio wave reflector was moved behind him/her. The hand movement graphs were compared to the graphs of the broadband radio frequency (RF) meter.

Reactions to standing waves	9 persons	Hand movement graphs include features like graphs of RF-meter.
Possible reaction	6 persons	Changes in the graphs but no correlation to RF-meter.
No reaction	14 persons	Only small noise like changes in the graphs.

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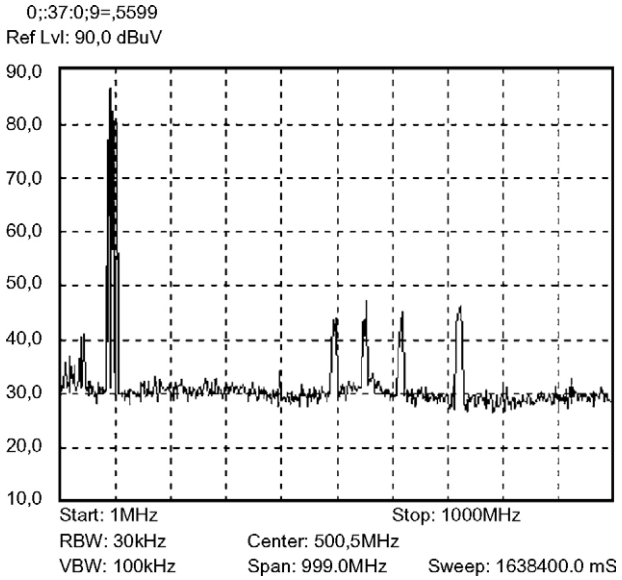

Fig. 3. Spectrum 1–1000 MHz at the test place. The highest peaks at the left are FM-radio broadcasting signals and the four lower peaks in the middle are the digital TV signals. Because the measurement was made with 1.5 m dipoles, signals near 100 MHz are more prominent because of antenna resonance.

incoming radio wave. The experimental maximum whole body resonance frequency is lower than the resonance frequency for an ideal half wave dipole antenna [11]. The whole body resonance length of a human at the frequencies of 80–108 MHz applied to FM broadcasting is about 1.1–1.5 m. Because in this experiment the test subjects were standing and the 100 MHz FM-radio signals and TV signals at higher frequencies are horizontally polarized, the absorption is obviously higher in the shoulder area. The distance between two maximums of the 100 MHz standing wave is 1.5 m. The half

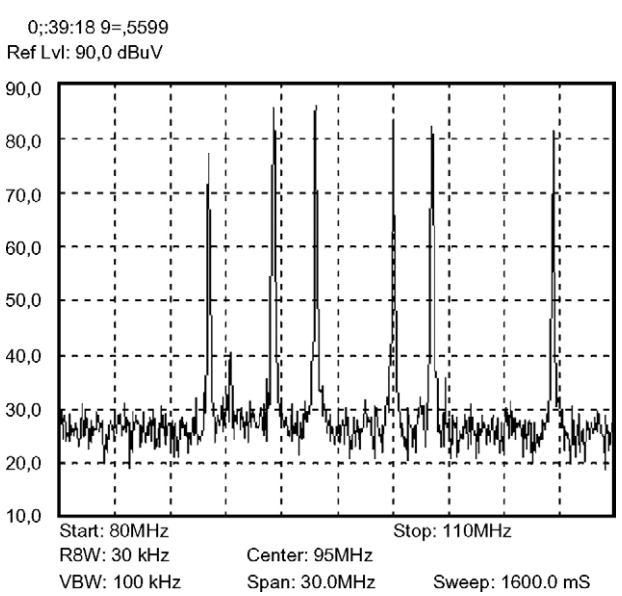

Fig. 4. Spectrum of the FM-radio broadcasting at the test place. Six channels were sending and the maximum electric field intensity was 85 dB μV.

waves of local digital TV signals (500–700 MHz) are only about 20–30 cm. This means that there can be many maximums of standing waves of TV signals in the body at the same time, even near the reflector.

The biggest variation in the local field intensity was caused by the FM broadcasting. There were 6 channels in the tower. Because of different wave lengths, the standing waves near the reflector are at the same phase and they amplify each other, but further away, the phases are mixed and so the amplitude of the summed standing waves is smaller.

With this experiment, we cannot exactly say where the reaction occurs, in limbs, muscles or in the head. It is possible that a change of intensity in standing radiowaves causes a small change in the nerve-muscle permeability of the nerve signal. The person feels it like a spontaneous muscle contraction. His hands are moving away and closer when the standing waves are passing. By some persons, the distance from hand to hand varied 0–60 cm. That means that some of muscles in arms and shoulders should react.

The spectrum contains many frequencies of electromagnetic radiation. The radiation is not only coming from the nearest tower, and it is impossible to clean the test area from other waves. This experiment was made at rural area, but even there, the private hand held telephone signals cause interferences to RF-instruments.

4. Conclusions

Sensitive persons seem to react to crossing standing waves of the FM-radio or TV broadcasting signals. The reactions were apparently initiated by RFR near reflecting objects, but they became more random in very weak variations of total field intensity. In any case, individuals are different, and in natural situations many sources interfere with each other.

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Cell phone radiation: Evidence from ELF and RF studies supporting more inclusive risk identification and assessment☆

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Abstract

Many national and international exposure standards for maximum radiation exposure from the use of cell phone and other similar portable devices are ultimately based on the production of heat particularly in regions of the head, that is, thermal effects (TE). The recent elevation in some countries of the allowable exposure, that is, averaging the exposure that occurs in a 6 min period over 10 g of tissue rather than over 1 g allows for greater heating in small portions of the 10-g volume compared to the exposure that would be allowed averaged over 1-g volume. There is concern that 'hot' spots, that is, momentary higher intensities, could occur in portions of the 10-g tissue piece, might have adverse consequences, particularly in brain tissue.

There is another concern about exposure to cell phone radiation that has been virtually ignored except for the National Council of Radiation Protection and Measurements (NCRP) advice given in a publication in 1986 [National Council for Radiation Protection and Measurements, Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Fields, National Council for Radiation Protection and Measurements, 1986, 400 pp.]. This NCRP review and guidance explicitly acknowledge the existence of non-thermal effects (NTE), and included provisions for reduced maximum-allowable limits should certain radiation characteristics occur during the exposure.

If we are to take most current national and international exposure standards as completely protective of thermal injury for acute exposure only (6 min time period) then the recent evidence from epidemiological studies associating increases in brain and head cancers with increased cell phone use per day and per year over 8–12 years, raises concerns about the possible health consequences on NTE first acknowledged in the NCRP 1986 report [National Council for Radiation Protection and Measurements, Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Fields, National Council for Radiation Protection and Measurements, 1986, 400 pp.].

This paper will review some of the salient evidence that demonstrates the existence of NTE and the exposure complexities that must be considered and understood to provide appropriate, more thorough evaluation and guidance for future studies and for assessment of potential health consequences. Unfortunately, this paper is necessary because most national and international reviews of the research area since the 1986 report [National Council for Radiation Protection and Measurements, Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Fields, National Council for Radiation Protection and Measurements, 1986, 400 pp.] have not included scientists with expertise in NTE, or given appropriate attention to their requests to include NTE in the establishment of public-health-based radiation exposure standards. Thus, those standards are limited because they are not comprehensive.
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Keywords: Non-thermal effects; Electromagnetic fields; Exposure standards

1. Introduction

1.1. The current approach to exposure limits (based on heating and electric current flow in tissues)

It is universally accepted that radiofrequency radiation (RFR) can cause tissue heating (thermal effects, TE) and that extremely low-frequency (ELF) fields, e.g., 50

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and 60 Hz, can cause electrical current flows that shock and even damage or destroy tissues. These factors alone are the underlying bases for present exposure standards. EMF exposures that cause biological effects at intensities that do not cause obvious thermal changes, that is, non-thermal effects (NTE), have been widely reported in the scientific literature since the 1970s including beneficial applications in development and repair processes. The current public safety limits do not take modulation into account and thus are no longer sufficiently protective of public health where chronic exposure to pulsed or pulse-modulated signal is involved, and where sub-populations of more susceptible individuals may be at risk from such exposures.

1.2. Modulation as a critical element

Modulation signals are one important component in the delivery of EMF signals to which cells, tissues, organs and individuals can respond biologically. At the most basic level, modulation can be considered a pattern of pulses or repeating signals which have specific meaning in defining that signal apart from all others. Modulated signals have a specific 'beat' defined by how the signal varies periodically or aperiodically over time. Pulsed signals occur in an on–off pattern, which can be either smooth and rhythmic, or sharply pulsed in quick bursts. Amplitude and frequency modulation involves two very different processes where the high-frequency signal, called the carrier wave, has a lower frequency signal that is superimposed on or 'rides' on the carrier frequency. In amplitude modulation, the lower frequency signal is embedded on the carrier wave as changes in its amplitude as a function of time, whereas in frequency modulation, the lower frequency signal is embedded as slight changes in the frequency of the carrier wave. Each type of low-frequency modulation conveys specific 'information', and some modulation patterns are more effective (more bioactive) than others depending on the biological reactivity of the exposed material. This enhanced interaction can be a good thing for therapeutic purposes in medicine, but can be deleterious to health where such signals could stimulate disease-related processes, such as increased cell proliferation in precancerous lesions. Modulation signals may interfere with normal, non-linear biological functions. More recent studies of modulated RF signals report changes in human cognition, reaction time, brainwave activity, sleep disruption and immune function. These studies have tested the RF and ELF-modulated RF signals from emerging wireless technologies (cell phones) that rely on pulse-modulated RF to transmit signals. Thus modulation can be considered as information content embedded in the higher frequency carrier wave that may have biological consequences beyond any effect from the carrier wave directly.

In mobile telephony, for example, modulation is one of the underlying ways to categorize the radiofrequency signal of one telecom carrier from another (TDMA from CDMA from GSM). Modulation is likely a key factor in determining whether and when biological reactivity might be occurring, for example in the new technologies which make use of modulated signals, some modulation (the packaging for delivery for an EMF 'message') may be bioactive, for example, when frequencies are similar to those found in brain wave patterns. If a new technology happens to use brain wave frequencies, the chances are higher that it will have effects, in comparison, for example, to choosing some lower or higher modulation frequency to carry the same EMF information to its target.

This chapter will show that other EMF factors may also be involved in determining if a given low-frequency signal directly, or as a modulation of a radiofrequency wave, can be bioactive. Such is the evolving nature of information about modulation. It argues for great care in defining standards that are intended to be protective of public health and well-being. This chapter will also describe some features of exposure and physiological conditions that are required in general for non-thermal effects to be produced, and specifically *to illustrate how modulation is a fundamental factor which should be taken into account in public safety standards*.

2. Laboratory evidence

Published laboratory studies have provided evidence for more than 40 years on bioeffects at much lower intensities than cited in the various widely publicized guidelines for limits to prevent harmful effects. Many of these reports show EMF-caused changes in processes associated with cell growth control, differentiation and proliferation, that are biological processes of considerable interest to physicians for potential therapeutic applications and for scientists who study the molecular and cellular basis of cancer. EMF effects have been reported in gene induction, transmembrane signaling cascades, gap junction communication, immune system action, rates of cell transformation, breast cancer cell growth, regeneration of damaged nerves and recalcitrant bone-fracture healing. These reports have cell growth control as a common theme. Other more recent studies on brainwave activity, cognition and human reaction time lend credence to modulation (pulsed RF and ELF-modulated RF) as a concern for wireless technologies, most prominently from cell phone use.

In the process of studying non-thermal biological effects, various exposure parameters have been shown to influence whether or not a specific EMF can cause a biological effect, including intensity, frequency, the co-incidence of the static magnetic field (both the natural earth's magnetic field and anthropogenic fields), the presence of the electrical field, the magnetic field, or their combination, and whether EMF is sinusoidal, pulsed or in more com-

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plex wave forms. These parameters will be discussed below.

Experimental results will be used to illustrate the influence of each EMF parameter, while also demonstrating that it is highly unlikely the effects are due to EMF-caused current flow or heating.

2.1. Initial studies that drew attention to NTE

Several papers in the 1960s and early 1970s reported that ELF fields could alter circadian rhythms in laboratory animals and humans. In the latter 1960s, a paper by Hamer [2] reported that the EMF environment in planned space capsules could cause human response time changes, i.e., the interval between a signal and the human response. Subsequent experiments by a research group led by Adey were conducted with monkeys, and showed similar response time changes and also EEG pattern changes [3,4]. The investigators shifted the research subject to cats and decided they needed to use a radiofrequency field to carry the ELF signal into the cat brain, and observed EEG pattern changes, ability to sense and behaviorally respond to the ELF component of RFR, and the ability of minor electric current to stimulate the release of an inhibitory neurotransmitter, GABA, and simultaneous release of a surrogate measure, calcium ions, from the cortex [5,6]. At this time Bawin, a member of the research group, adopted newly hatch chickens as sources of brain tissue and observed changes in the release of calcium ions from in vitro specimens as a function of ELF frequency directly or as amplitude modulation ('am') of RFR (RFRam) [7–11]. Tests of both EMF frequency and intensity dependences demonstrated a single sensitive region (termed 'window') over the range of frequency and intensity examined. This series of papers showed that EMF-induced changes could occur in several species (human, monkey, cat and chicken), that calcium ions could be used as surrogate measures for a neurotransmitter, that ELF fields could produce effects similar to RFRam (note: without the 'am', there was no effect although the RFR intensity was the same), and that the dose and frequency response consisted of a single sensitivity window.

Subsequent, independent research groups published a series of papers replicating and extending this earlier work. Initial studies by Blackman, Joines and colleagues [12–25] used the same chick brain assay system as Bawin and colleagues. These papers reported multiple windows in intensity and in frequency within which calcium changes were observed in the chick brain experimental systems under EMF exposure. Three other independent groups offered confirmation of these results by reporting intensity and frequency windows for calcium, neurotransmitter or enolase release under EMF exposure of human and animal nervous system-derived cells in vitro by Dutta et al. [26–29], of rat pancreatic tissue slices by Albert et al. [30], and of frog heart by Schwartz et al. [31] but not frog-heart atrial strips in vitro [32]. This series of papers showed that multiple frequency and intensity windows were a common phenomenon that required the development of new theoretical concepts to provide a mechanism of action paradigm.

2.2. Refined laboratory studies reveal more details

Additional aspects of the EMF experiments with the chick brain described by Blackman and colleagues, above, also revealed critical co-factors that influenced the action of EMF to cause changes in calcium release, including the influence of the local static magnetic field, and the influence of physico-chemical parameters, such as pH, temperature and the ionic strength of the bathing solution surrounding the brain tissue during exposure. This information provides clues for and constraints on any theoretical mechanism that is to be developed to explain the phenomenon. Most current theories ignore these parameters that need to be monitored and controlled for EMF exposure to produce NTE. These factors demonstrate that the current risk assessment paradigms, which ignore them, are incomplete and thus may not provide the level of protection currently assumed.

2.3. Sensitivity of developing organisms

An additional study was also conducted to determine if EMF exposure of chicken eggs while the embryo was developing could influence the response of brain tissue from the newly hatched chickens. The detailed set of frequency and intensity combinations under which effects were observed, were all obtained from hatched chickens whose eggs were incubated for 21 days in an electrically heated chamber containing 60-Hz fields. Thus tests were performed to determine if the 60-Hz frequency of ELF fields (10 V/m in air) during incubation, i.e., during embryogenesis and organogenesis, would alter the subsequent calcium release responses of the brain tissue to EMF exposure. The reports of Blackman et al. [19] and Joines et al. [25] showed that the brain tissue response was changed when the field during the incubation period was 50 Hz rather than 60 Hz. This result is consistent with an anecdotal report of adult humans, institutionalized because of chemical sensitivities, who were also responsive to the frequency of power-line EM fields that were present in the countries where they were born and raised [33]. This information indicates there may be animal and human exposure situations where EMF imprinting during development could be an important factor in laboratory and epidemiological situations. EMF imprinting, which may only become manifest when a human is subjected to chemical or biological stresses, could reduce ability to fight disease and toxic insult from environmental pollution, resulting in a population in need of more medical services, with resulting lost days at work.

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3. Fundamental exposure parameters—to be considered when establishing a mode (or mechanism) of action for non-thermal EMF-induced biological effects

3.1. Intensity

There are numerous reports of biological effects that show intensity "windows", that is, regions of intensity that cause changes surrounded by higher and lower intensities that show no effects from exposure. One very clear effect by Blackman and colleagues is 16-Hz, sine wave-induced changes in calcium efflux from brain tissue in a test tube because it shows two very distinct and clearly separated intensity windows of effects surrounded by regions of intensities that caused no effects [17]. There are other reports for similar multiple windows of intensity in the radiofrequency range [22,26,29,31]. Note that calcium ions are a secondary signal transduction agent active in many cellular pathways. These results show that intensity windows exist, they display an unusual and unanticipated "non-linear" (non-linear and non-monotonic) phenomenon that has been ignored in all risk assessment and standard setting exercises, save the NCRP 1986 publication [1]. Protection from multiple intensity windows has never been incorporated into any risk assessment; to do so would call for a major change in thinking. These results mean that lower intensity is not necessarily less bioactive, or less harmful.

Multiple intensity windows appeared as an unexpected phenomenon in the late 1970s and 1980s. There has been one limited attempt to specifically model this phenomenon by Thompson et al. [34], which was reasonably successful. This modeling effort should be extended because there are publications from two independent research groups showing multiple intensity windows for 50, 147, and 450 MHz fields when amplitude modulated at 16 Hz using the calcium ion release endpoint in chicken brains, in vitro. The incident intensities (measured in air) for the windows at the different carrier frequencies do not align at the same values. However, Joines et al. [23,24] and Blackman et al. [20] noted the windows of intensity align across different carrier frequencies if one converts the incident intensity to the intensity expected within the sample at the brain surface. This conversion was accomplished by correcting for the different dielectric constants of the sample materials due to the different carrier frequencies. The uniqueness of this response provides a substantial clue to theoreticians but it is interesting and disappointing that no publications have appeared attempting to address this relationship. It is obvious that this phenomenon is one that needs further study.

3.2. Frequency

Frequency-dependent phenomena are common occurrences in nature. For example, the human ear only hears a portion of the sound that is in the environment, typically from 20 to 20,000 Hz, which is a frequency "window". Another biological frequency window can be observed for plants grown indoors. Given normal indoor lighting the plants may grow to produce lush vegetation but not produce flowers unless illuminated with a lamp that emits a different spectrum of light partially mimicking the light from the sun. Thus, frequency windows of response to various agents exist in biological systems from plants to homo sapiens.

In a similar manner, there are examples of EMF-caused biological effects that occur in a frequency-dependent manner that cannot be explained by current flow or heating. The examples include reports of calcium ion efflux from brain tissue in vitro by Blackman and Joines and colleagues at low frequency [15,19] and at high frequency modulated at low frequency [20,35,24]. An additional example of an unexpected result is by Liboff [36].

In addition, two apparently contradictory multiple-frequency exposure results provide examples of the unique and varied non-thermal interactions of EMF with biological systems. Litovitz and colleagues showed that an ELF sinusoidal signal could induce a biological response in a cell culture preparation, and that the addition of a noise signal of equal average intensity could block the effect caused by the sinusoidal signal, thereby negating the influence of the sinusoidal signal [37]. Similar noise canceling effects were observed using chick embryo preparations [38,39]. It was also shown that the biological effects caused by microwave exposures imitating cell phone signals could be mitigated by ELF noise [40]. However, this observation should not be generalized; a noise signal is not always benign. Milham and Morgan [41] showed that a sinusoidal ELF (60-Hz) signal was not associated with the induction of cancer in humans, but when that sinusoidal signal was augmented by a noise signal, basically transients that added higher frequencies, an increase in cancer was noted in humans exposed over the long-term. Thus, the addition of noise in this case was associated with the appearance of a health issue. Havas [42–44] has described other potential health problems associated with these higher frequency transients, termed "dirty power." The bioactive frequency regions observed in these studies have never been explicitly considered for use in any EMF risk assessments, thus demonstrating the incomplete nature of current exposure guideline limits.

There are also EMF frequency-dependent alterations in the action of nerve growth factor (NGF) to stimulate neurite outgrowth (growth of primitive axons or dendrites) from a peripheral-nerve-derived cell (PC-12) in culture shown by Blackman et al. [45,46] and by Trillo et al. [47]. The combined effect of frequency and intensity is also a common occurrence in both the analogous sound and the light examples given above. Too much or too little of either frequency or intensity show either no or undesirable effects. Similarly, Blackman et al. [15] has reported EMF responses composed of effect "islands" of intensity and frequency combinations, surrounded by a "sea" of intensity and frequency combinations of null effects. Although the mechanisms responsible

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for these effects have not been established, the effects represent a here-to-fore unknown phenomenon that may have complex ramifications for risk assessment and standard setting. Nerve growth and neurotransmitter release that can be altered by different combinations of EMF frequencies and intensities, especially in developing organisms like children, could conceivably produce over time a subsequent altered ability to successfully or fully respond behaviorally to natural stressors in the adult environment; research is urgently needed to test this possibility in animal systems.

Nevertheless, this phenomenon of frequency dependence is ignored in the development of present exposure standards. These standards rely primarily on biological responses to intensities within an arbitrarily defined engineering-based frequency bands, not biologically based response bands, and are solely based on an energy deposition determinations.

4. Static magnetic field—a completely unexpected complexity

The magnetic field of the earth at any given location has a relatively constant intensity as a function of time. However, the intensity value, and the inclination of the field with respect to the gravity vector, varies considerable over the face of the earth. More locally, these features of the earth's magnetic field can also vary by more than 20% inside manufactured structures, particularly those with steel support structures.

At the Bioelectromagnetics Society annual meeting in 1984 [48], Blackman revealed his group's discovery that the intensity of the static magnetic field could establish and define those oscillatory frequencies that would cause changes in calcium ion release in his chick brain preparation. This result was further discussed at a NATO Advanced Research workshop in Erice, Italy in the fall of 1984 and by publications from that meeting and subsequent research: Blackman et al. [14,18] and Liboff et al. [36,49,50]. Substantial additional research on this feature was reported by Liboff and colleagues [51,52,50]. Blackman et al. also reported on the importance of the relative orientation of the static magnetic field vector to the oscillating magnetic field vector [21] and demonstrated a reverse biological response could occur depending on parallel or perpendicular orientations of the static and oscillating magnetic fields [53].

There have been many attempts to explain this phenomenon by a number of research teams led by Smith [49], Blackman [15], Liboff [36,54], Lednev [55], Blanchard [56], Zhadin [57], del Giudice [58], Binhi [59–62], and Matronchik [63] but none has been universally accepted. Nevertheless, experimental results continued to report static and oscillating field dependencies for non-thermally induced biological effects in studies led by Zhadin [64,65], Vorobyov [66], Baureus Koch [67], Sarimov [68], Prato [69,70], Comisso [71], and Novikov [72].

With this accumulation of reports from independent, international researchers, it is now clear that if a biological response depends on the static magnetic field intensity, and even its orientation with respect to an oscillating field, then the conditions necessary to reproduce the phenomenon are very specific and might easily escape detection (see for example, Blackman and Most [73]. The consequences of these results are that there may be exposure situations that are truly detrimental (or beneficial) to organisms, but that are insufficiently common on a large scale that they would not be observed in epidemiological studies; they need to be studied under controlled laboratory conditions to determine impact on health and wellbeing.

5. Electric and magnetic components—both biological active with different consequences

Both the electric and the magnetic components have been shown to directly and independently cause biological changes. There is one report that clearly distinguishes the distinct biological responses caused by the electric field and by the magnetic field. Marron et al. [74] show that electric field exposure can increase the negative surface charge density of an amoeba, Physarum polycephalum, and that magnetic field exposure of the same organism causes changes in the surface of the organism to reduce its hydrophobic character. Other scientists have used concentric growth surfaces of different radii and vertical magnetic fields perpendicular to the growth surface to determine if the magnetic or the induced electric component is the agent causing biological change. Liburdy et al. [75], examining calcium influx in lymphocytes, and Greene et al. [76], monitoring ornithine decarboxylase (ODC) activity in cell culture, showed that the induced electric component was responsible for their results. In contrast, Blackman et al. [77,78] monitoring neurite outgrowth from two different clones of PC-12 cells and using the same exposure technique used by Liburdy and by Greene showed the magnetic component was the critical agent in their experiments. EMF-induced changes on the cell surface, where it interacts with its environment, can dramatically alter the homeostatic mechanisms in tissues, whereas changes in ODC activity are associated with the induction of cell proliferation, a desirable outcome if one is concerned about wound healing, but undesirable if the concern is tumor cell growth. This information demonstrates the multiple, different ways that EMF can affect biological systems. Present analyses for risk assessment and standard setting have ignored this information, thus making their conclusions of limited value.

6. Sine and pulsed waves—like different programs on a radio broadcast station

Important characteristics of pulsed waves that have been reported to influence biological processes include the following: (1) frequency, (2) pulse width, (3) intensity, (4) rise and fall time, and (5) the frequency, if any, within the pulse ON

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time. Chiabrera et al. [79] showed that pulsed fields caused de-differentiation of amphibian red blood cells. Scarfi et al. [80] showed enhanced micronuclei formation in lymphocytes of patients with Turner's syndrome (only one X chromosome) but no change in micronuclei formation when the lymphocytes were exposed to sine waves (Scarfi et al. [81]). Takahashi et al. [82] monitored thymidine incorporation in Chinese hamster cells and explored the influence of pulse frequency (two windows of enhancement reported), pulse width (one window of enhancement reported) and intensity (two windows of enhancement reported followed by a reduction in incorporation). Ubeda et al. [83] showed the influence of difference rise and fall times of pulsed waves on chick embryo development.

6.1. Importance for risk assessment

It is important to note that the frequency spectrum of pulsed waves can be represented by a sum of sine waves which, to borrow a chemical analogy, would represent a mixture of chemicals, anyone of which could be biologically active. Risk assessment and exposure limits have been established for specific chemicals or chemical classes of compounds that have been shown to cause undesirable biological effects. Risk assessors and the general public are sophisticated enough to recognize that it is impossible to declare all chemicals safe or hazardous; consider the difference between food and poisons, both of which are chemicals. A similar situation occurs for EMF; it is critical to determine which combinations of EMF conditions have the potential to cause biological harm and which do not.

Obviously, pulse wave exposures represent an entire genre of exposure conditions, with additional difficulty for exact independent replication of exposures, and thus of results, but with increased opportunities for the production of biological effects. Current standards were not developed with explicit knowledge of these additional consequences for biological responses.

7. Mechanisms

Two papers have the possibility of advancing understanding in this research area. Chiabrera et al. [84] created a theoretical model for EMF effects on an ion's interaction with protein that includes the influence of thermal energy and of metabolism. Before this publication, theoreticians assumed that biological effects in living systems could not occur if the electric signal is below the signal caused by thermal noise, in spite of experimental evidence to the contrary. In this paper, the authors show that this limitation is not absolute, and that different amounts of metabolic energy can influence the amount and parametric response of biological systems to EMF. The second paper, by Marino et al. [85], presents a new analytical approach to examine endpoints in systems exposed to EMF. The authors, focusing on exposure-induced lymphoid phenotypes, report that EMF may not cause changes in the mean values of endpoints, but by using recurrence analysis, they capture exposure-induced, statistically significant, non-linear movements of the endpoints to either side of the mean endpoint value. They provide further evidence using immunological endpoints from exposed and sham treated mice [86–88]. Additional research has emerged from this laboratory on EMF-induced animal and human brain activity changes that provides more evidence for the value of their research approach (Marino et al. [89–92], Kolomytkin et al. [93] and Carrubba et al. [94–98]). Further advanced theoretical and experimental studies of relevance to non-thermal biological effects are emerging; see for example reports by Binhi et al. [59–62], Zhadin et al. [64,99,65], and Novikov et al. [72]. *It is apparent that much remains to be examined and explained in EMF biological effects research through more creative methods of analysis than have been used before. The models described above need to be incorporated into risk assessment determinations.*

8. Problems with current risk assessments—observations of effects are segregated by artificial frequency bands that ignore modulation

One fundamental limitation of most reviews of EMF biological effects is that exposures are segregated by the physical (engineering/technical) concept of frequency bands favored by the engineering community. This is a default approach that follows the historical context established by the incremental addition of newer technologies that generate increasingly higher frequencies. However, this approach fails to consider unique responses from biological systems that are widely reported at various combinations of frequencies, modulations and intensities.

When common biological responses are observed without regard for the particular, engineering-defined EMF frequency band in which the effects occur, this reorganization of the results can highlight the commonalities in biological responses caused by exposures to EMF across the different engineering-defined frequency bands. An attempt to introduce this concept to escape the limitations of the engineering-defined structure occurred with the development of the 1986 NCRP radiofrequency exposure guidelines because published papers from the early 1970s to the mid 1980s (to be discussed below) demonstrated the need to include amplitude modulation as a factor in setting of maximum exposure limits. The 1986 NCRP guideline [1] was the one and only risk evaluation that included an exception for modulated fields.

The current research and risk assessment attempts are no longer tenable. The 3-year delay in the expected report of the 7-year Interphone study results has made this epidemiological approach a 10-year long effort, and the specific exposure conditions, due to improved technology, have changed so that the results may no longer be applicable to the current

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exposure situation. It is unproductive to continue to fund epidemiological studies of people who are exposed to a wide variety of diversified, uncontrolled, and poorly characterized EMF in their natural and work environments. In place of the funding of more epidemiological studies should be funding to support controlled laboratory studies to focus on the underlying processes responsible for the NTE described above, so that mechanisms or modes of action can be developed to provide a theoretical framework to further identify, characterize and unify the action of the heretofore ignored exposure parameters shown to be important.

8.1. Potential explanation for the failure to optimize research in EMF biological effects

Unfortunately, risk evaluations following the 1986 NCRP example [1], returned to the former engineering-defined analysis conditions, in part because scientists who reported non-thermal effects were not placed on the review committees, and in the terms of Slovic [100] "Risk assessment is inherently subjective and represent a blend of science and judgment with important psychological, social, cultural, and political factors. . . . Whoever controls the definition of risk controls the rational solution to the problem at hand. . . . Defining risk is thus an exercise in power." It appears that by excluding scientists experienced with producing non-thermal biological effects, the usually sound judgment by the selected committees was severely limited in its breadth-of-experience, thereby causing the members to retreat to their own limited areas of expertise when forced to make judgments, as described by Slovic [100], "Public views are also influenced by worldviews, ideologies, and values; so are scientists' views, particularly when they are working at limits of their expertise." The current practice of segregating scientific investigations (and resulting public health limits) by artificial divisions of frequency dramatically dilutes the impact of the basic science results, thereby reducing and distorting the weight of evidence in any evaluation process (see evaluations of bias by Havas [101], referring to NRC 1997 [102] compared to NIEHS 1998 [103] and NIEHS 1999 [104]).

9. Suggested research

Are there substitute approaches that would improve on the health-effects evaluation situation? As mentioned above, it may be useful in certain cases to develop a biologically based clustering of the data to focus on and enrich understanding of certain aspects of biological responses. Some examples to consider for biological clustering include: (1) EMF features, such as frequency and intensity inter-dependencies, (2) common co-factors, such as the earth's magnetic field or co-incident application of chemical agents to perturb and perhaps sensitize the biological system to EMF, or (3) physiological state of the biological specimen, such as age or sensitive sub-populations, including genetic predisposition as described by Fedrowitz et al. [105,106], and for human populations, recently reported by Yang et al. [107].

To determine if this approach has merit, one could combine reports of biological effects found in the ELF (including sub-ELF) band with effects found in the RF band when the RF exposures are amplitude modulated (AM) using frequencies in the ELF band. The following data should be used: (a) human response time changes under ELF exposure [2], (b) monkey response time and EEG changes under ELF exposure [3,4], (c) cat brain EEG, GABA and calcium ion changes induced by ELF and AM-RF [8,9,7,10,6,11,108,5], (d) calcium ion changes in chick brain tissue under ELF and AM-RF [8,9,7,10,13–15,21,16–18,12,19,20,22,35,23–25,11], and (e) calcium changes under AM-RF in brain cells in culture [26–28] and in frog heart under AM-RF [31]. The potential usefulness of applying biological clustering in the example given above even though AM is used, is that the results may have relevance to assist in the examination of some of the effects reportedly caused by cellular phone exposures which include more complex types of modulation of RF. This suggestion is reasonable because three groups later reported human responses to cell phone emissions that include changes in reaction times – Preece et al. [109,110], Koivisto et al. [111,112] and Krause et al. [113,114] – or to brain wave potentials that may be associated with reaction time changes—Freude et al. [115,116].

Subsequently, Preece et al. [117] tested cognitive function in children and found a trend, but not a statistically significant change in simple reaction time under exposure, perhaps because he applied a Bonferroni correction to his data (alpha for significance was required to be less than 0.0023). It would appear that a change in the experimental protocol might provide a more definitive test of the influence of exposure on simple reaction time because it is known that a Bonferroni correction is a particularly severe test of statistical significance, or as the author observed, "a particularly conservative criterion."

Krause et al. [118] examined cognitive activity by observing oscillatory EEG activity in children exposed to cell phone radiation while performing an auditory memory task and reported exposure related changes in the ~4–8 Hz EEG frequencies during memory encoding, and changes in that range and also ~15 Hz during recognition. The investigators also examined cognitive processing, an auditory memory task or a visual working memory task, in adults exposed to CW or pulsed cell phone radiation on either the right or left side of the head, and reported modest changes in brain EEG activity in the ~4–8 Hz region, compared to CW exposure, but with caveats that no behavior changes were observed, and that the data were varying, unsystematic and inconsistent with previous reports (Krause et al. [119]). Haarala and colleagues conducted an extensive series of experiments, examining reaction time [120], short-term memory [121], short-term memory in children [122], and right versus left hemisphere exposure [123]. Although these studies did not

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support the positive effects from exposure reported by others, they provided possible explanations for the apparent lack of agreement.

Other research groups have also examined the effects of cell phone radiation on the central nervous system, including Borbely et al. [124], Huber et al. [125], Loughran et al. [126], and D'Costa et al. [127], who found changes in sleep EEG patterns and other measures during or after short-term exposures, while others, such as Fritzer et al. [128] exposed for longer time periods found no changes in sleep parameters, EEG power spectra, correlation dimension nor cognitive function. The work of Pritchard [129] served as the basis to examining correlation dimensions, which is opening a potentially fertile avenue for investigation. Although this approach provides more indepth information on ongoing processes and function, it has not yet been used to address potential consequences associated with long-term cell phone use.

The papers published in the 1960s through 1991, described in earlier sections of this paper, foreshadowed the more recent publications in 1999 through 2008 showing response time changes, or associated measures, in human subjects during exposure to cell phone-generated radiation. It is unfortunate that essentially none of the earlier studies was acknowledged in these recent reports on cognition, reaction time and other measures of central nervous system processes. Without guidance from this extensive earlier work, particularly those demonstrating the variety of exposure parameter spaces that must be controlled to produce repeatable experiments, the development of the mechanistic bases for non-thermal effects from EMF exposures will be substantially delayed. The omission of the recognition of the exposure conditions that affect the biological outcomes continues as recently as the National Academy of Science 2009 publication [130] of future directions for research, which emphasizes the modest perspective in the results from committee members working at the limits of expertise, as anticipated by Slovic [100].

Let us hope that subsequent national and international committees that consider future directions for EMF research include members who have performed and reported non-thermal effects, in order to provide a broader perspective to develop programs that will more expeditiously address potential health problems as well as to provide guidance to industry on prudent procedures to establish for their technologies.

At present, we are left with a recommendation voiced in 1989 by Abelson [131] in an editorial in Science Magazine that addressed electric power-specific EMF, but is applicable to higher frequency EMF as well, to "adopt a prudent avoidance strategy" by "adopting those which look to be 'prudent' investments given their cost and our current level of scientific understanding about possible risks."

10. Conclusions

There is substantial scientific evidence that some modulated fields (pulsed or repeated signals) are bioactive, which increases the likelihood that they could have health impacts with chronic exposure even at very low exposure levels. Modulation signals may interfere with normal, non-linear biological processes. Modulation is a fundamental factor that should be taken into account in new public safety standards; at present it is not even a contributing factor. To properly evaluate the biological and health impacts of exposure to modulated RFR (carrier waves), it is also essential to study the impact of the modulating signal (lower frequency fields or ELF-modulated RF). Current standards have ignored modulation as a factor in human health impacts, and thus are inadequate in the protection of the public in terms of chronic exposure to some forms of ELF-modulated RF signals. The current IEEE and ICNIRP standards are not sufficiently protective of public health with respect to chronic exposure to modulated fields (particularly new technologies that are pulse-modulated and heavily used in cellular telephony). The collective papers on modulation appear to be omitted from consideration in the recent WHO and IEEE science reviews. This body of research has been ignored by current standard setting bodies that rely only on traditional energy-based (thermal) concepts. More laboratory as opposed to epidemiological research is needed to determine which modulation factors, and combinations are bioactive and deleterious at low intensities, and are likely to result in disease-related processes and/or health risks; however this should not delay preventative actions supporting public health and wellness. If signals need to be modulated in the development of new wireless technologies, for example, it makes sense to use what existing scientific information is available to avoid the most obviously deleterious exposure parameters and select others that may be less likely to interfere with normal biological processes in life. The current membership on Risk Assessment committees needs to be made more inclusive, by adding scientists experienced with producing non-thermal biological effects. The current practice of segregating scientific investigations (and resulting public health limits) by artificial, engineering-based divisions of frequency needs to be changed because this approach dramatically dilutes the impact of the basic science results and eliminates consideration of modulation signals, thereby reducing and distorting the weight of evidence in any evaluation process.

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Apparent decreases in Swedish public health indicators after 1997—Are they due to improved diagnostics or to environmental factors?

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Abstract

The object of this work was to review recent trends in public health in Sweden. Data on different adverse health indicators were collected from official Swedish registries. We found that population health generally improved during the early 1990s but suddenly started to deteriorate from 1997 onwards. This quite dramatic change is not likely to be explained only by improved diagnostics but physical causes need immediately to be searched for. A connection with the increasing exposure of the population to GHz radiation from mobile phones, base stations and other communication technologies cannot be ruled out.

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Keywords: Alzheimer's disease; Heart malformations; Lung cancer; Melanoma; Prostata carcinoma; Traffic accidents; Mobile phone speech time

1. Introduction

During the first half of the 1990s, the Swedish population appeared increasingly healthy. Sick leave registrations decreased; in addition, lung cancer among older men steadily decreased and the incidence of prostate cancer levelled out, becoming stable or slightly decreasing between 1993 and 1997. In Stockholm, even the number of traffic accidents with injuries went down each year from 1985 to 1996. Mortality due to Alzheimer's disease increased in the early 1980s, but remained steady at 2.5–4 per 100,000 person-years (age standardized) from 1990 to 1997.

Objective of the present study: After 1997, public health appeared to decline markedly. Was this decrease the result of improvements in detection and diagnosis, or did maladies actually increase? In this paper, we take a look at several health trends, one by one, and analyze the suggested causes underlying the adverse health- and traffic safety indicators.

2. Materials and methods

All data were retrieved from the official databases of the National Health and Welfare Board (Socialstyrelsen; SoS) and of the Swedish Road Administration (Vägverket; VV). Hallberg and Johansson (2004) have presented worrying trends related to public health in Sweden [1]. Hallberg (2007) showed that many adverse health indicators were worse in sparsely populated areas, as hypothesized caused by higher average output power from mobile phones in those areas [2].

3. Results and discussion

1. Lung cancer among elderly men increased markedly beginning after 1997 (Fig. 1). For men aged 80–84 years, the incidence increased from 160 to 230/100,000. For men aged 85+, the incidence increased from 95 to a high of 180/100,000 in 2005. The SoS has not publicly offered any explanation for these increases or commented on this matter.
2. In 1997, the incidence of prostate cancer abruptly increased in all age groups (Fig. 2). In Stockholm, the number of cases in men aged 50–59 stayed fairly stable

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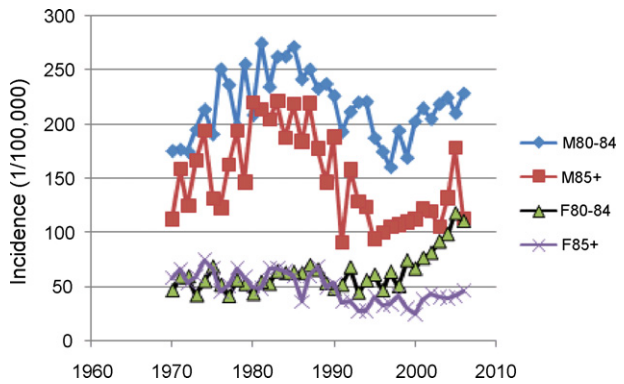

Fig. 1. Lung cancer in the elderly (male (M) and female (F)) has increased in Sweden since 1997.

at around 30 cases per year up to 1996, despite the fact that PSA tests were used routinely starting in 1991. After 1996, when 33 cases of prostate cancer were reported, the number of cases increased to around 300 per year in 2004 and 2005. SoS originally suggested that the apparent increase in prostate cancer was due to the improved diagnostic capabilities of the PSA test. When asked again, the SoS said, "It cannot, however, be ruled out that a certain increase would have been noticed even without these PSA tests, but we don't know how large this increase would have been." Notably, however, the step-like increase in prostate cancer did not coincide with the introduction of the PSA test in 1991.

3. For several decades, the rate of skin melanoma was very stable among younger people (<50 years), despite publicity about the dangers of sun exposure. However, after 2000 the incidence of melanoma of the head and neck region suddenly started to increase in this population (Fig. 3). Simultaneously, the rate of more benign skin tumours dropped, and the sum total of tumours and melanoma continued to increase. However, small carcinomas that would previously have developed into relatively benign tumours now seem to increasingly develop into melanoma. SoS has not commented on this in their reports.

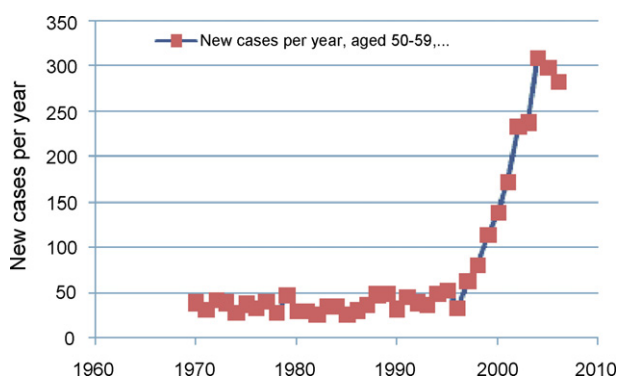

Fig. 2. The number of newly reported cases of prostate cancer in men aged 50–59 years in Stockholm County, Sweden.

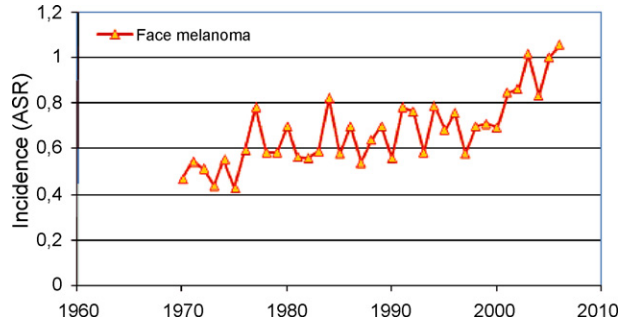

Fig. 3. Melanoma of the face has increased in Sweden among people <60 years since 2000.

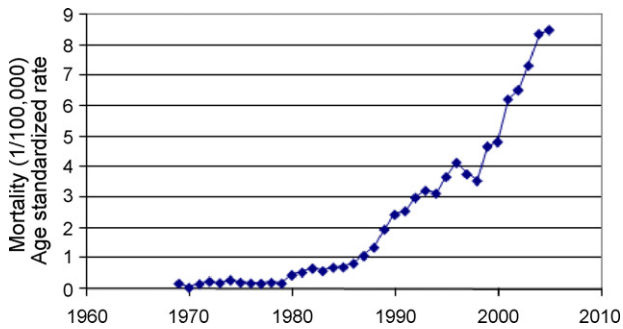

Fig. 4. Alzheimer's mortality has increased steeply since 1998 in Sweden.

4. Mortality associated with Alzheimer's disease has increased dramatically since 1998 (Fig. 4). Today, the incidence is 9/100,000, an increase of 300% in 10 years. When queried, the SoS suggested that this increase can be attributed to an increase in the practice of declaring Alzheimer's disease as the cause of death when signing the death certificate. SoS also claims that there are no grounds for stating that mortality has actually increased. However, a thorough analysis of the data indicates that there is an increase in mortality in older people with this disease [3].
5. In 1985, the number of people seriously injured in Stockholm traffic accidents was around 650. Subsequently, there was a decrease in injuries to a low of 350 in 1997. After 1997, the number of people injured annually started

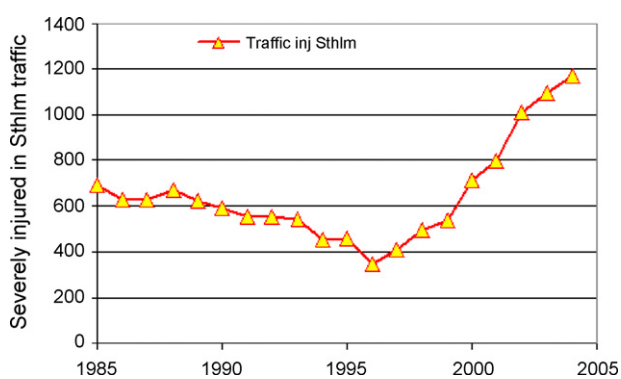

Fig. 5. Traffic injuries in Stockholm have increased since 1997.

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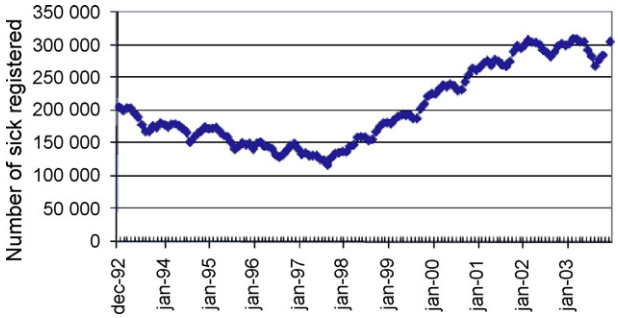

Fig. 6. The number of people in Sweden registered as sick suddenly increased starting in September 1997.

increasing, reaching 1200 in 2005 (Fig. 5). According to VV, this trend is partly the result of the introduction of a better reporting system in Stockholm. Nonetheless, the increasing number of people severely injured in Swedish traffic ended the downward trend observed until 1997: This number has rapidly increased since 2000. Today, VV reports that the number of people who were severely injured per killed increased rapidly in Stockholm County in the time period 2000–2004.

6. The total number of people taking sick leave was just over 200,000 in 1992. This number decreased steadily to around 125,000 in September 1997. After that time, the trend broke, and we saw an increase to over 300,000 people registering as sick in 2003 (Fig. 6). The authorities have not given any explanation for this abrupt increase in the number of people who registered as sick. It is not likely due to improved diagnostics, but rather to the fact that more people needed to take sick leave. In November 2001, the leader of the KD party, Alf Svensson, commented that "sick-cheating" was one explanation. In contrast to earlier trends, the increase in sickness appears to be greater in more sparsely populated regions. In the beginning of the 80s, it was considered healthy to live in the countryside, since people were healthier there. A closer analysis of sick leave data in different counties shows that the Northern counties and the Gotland island were the last counties to show an increase in sick leave rates. These counties did not show increasing rates until February 1998. In contrast, the increase was observed early on in Blekinge and Kronoborg, where the increase was noticeable in September/October of 1997.
7. The number of new brain tumours in people >60 years old suddenly increased after 2000 (Fig. 7). This development paralleled the increase of melanoma in the face region of people <60 years. In general, the incidence of brain tumours is increasing most in more sparsely populated regions where mobile phones often need to use full output power [2,4].
8. The percentage of newborns with heart problems began to increase after 1998 (Fig. 8). It was recently reported that fetuses and neonates react to their mother's mobile phone use with an increased pulse rate and decreased blood flow [5]. Another report published in the well-known journal *Epidemiology* [6] suggests that such mobile phone use may also influence emotional development and may increase the risk of hyperactivity, behaviour problems, and relational problems with other children up to the time that children start school.

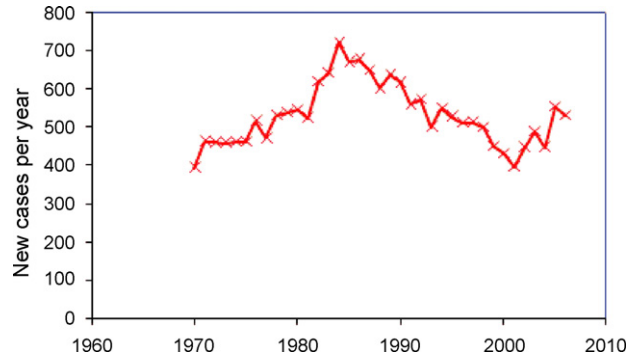

Fig. 7. Brain tumours among in the elderly (>60 years) have increased since 2001 in Sweden.

A dramatic environmental change took place in Sweden in the autumn of 1997. At this time, GSM 1800 MHz transmitters were put into use to increase transmission capacity, especially in urban areas, see Fig. 8. Much of the population began to be exposed to 1.8 GHz microwaves both at night and during the day. In the Stockholm area, people began to steer cars using only their right hands while holding the mobile phones by their left hands. The Post- and Telecom Administration states that GSM 1800 MHz began to be used in 1997, but has no information on starting months in different counties. When Telia were queried about starting dates

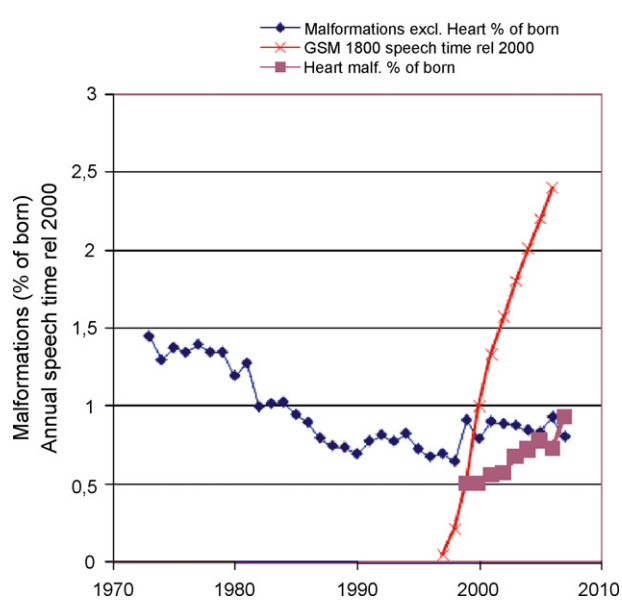

Fig. 8. The percentage of newborns with heart problems has increased since 1998 in Sweden. Also shown is the annual speech time in dual band mobile phones relative to year 2000. The down going trend of malformed newborns excluding heart problems is now broken since 1998.

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for transmitter operation, Telia responded that they will not release this information. "The reason is that this information reasonably has no association with sick registration levels in Sweden in 1997." In 2001, the roll-out of the 3G network started and the use of the higher and probably more biological hazardous frequency, around 2.1 GHz, increased. More details about relevant events in 1997 are described in reference [1].

4. Conclusion

The negative trends in public health indicators in Sweden are not fully explained by better diagnostics, better instrumentation, or better doctors. Because these indicators may reflect real world changes, efforts should be made, starting immediately, to determine the underlying cause or causes.

Conflict of interest

There is no conflict of interest known to the authors related to this work.

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Public health implications of wireless technologies

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Abstract

Global exposures to emerging wireless technologies from applications including mobile phones, cordless phones, DECT phones, WI-FI, WLAN, WiMAX, wireless internet, baby monitors, and others may present serious public health consequences. Evidence supporting a public health risk is documented in the BioInitiative Report. New, biologically based public exposure standards for chronic exposure to low-intensity exposures are warranted. Existing safety standards are obsolete because they are based solely on thermal effects from acute exposures. The rapidly expanding development of new wireless technologies and the long latency for the development of such serious diseases as brain cancers means that failure to take immediate action to reduce risks may result in an epidemic of potentially fatal diseases in the future. Regardless of whether or not the associations are causal, the strengths of the associations are sufficiently strong that in the opinion of the authors, taking action to reduce exposures is imperative, especially for the fetus and children. Such action is fully compatible with the precautionary principle, as enunciated by the Rio Declaration, the European Constitution Principle on Health (Section 3.1) and the European Union Treaties Article 174.
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Keywords: Wireless technology; Brain cancer; Radiofrequency; Cell phones; Wireless antenna facilities; Childrens' health

1. Introduction and background

Exposure to electromagnetic fields (EMF) has been linked to a variety of adverse health outcomes that may have significant public health consequences [1–13]. The most serious health endpoints that have been reported to be associated with extremely low frequency (ELF) and/or RF include childhood and adult leukemia, childhood and adult brain tumors, and increased risk of the neurodegenerative diseases, Alzheimer's and amyotrophic lateral sclerosis (ALS). In addition, there are reports of increased risk of breast cancer in both men and women, genotoxic effects (DNA damage and micronucleation), pathological leakage of the blood–brain barrier, altered immune function including increased allergic and inflammatory responses, miscarriage and some cardiovascular effects [1–13]. Insomnia (sleep disruption) is reported in studies of people living in very low-intensity RF environments with WI-FI and cell tower-level exposures [85–93]. Short-term effects on cognition, memory and learning, behavior, reaction time, attention and concentration, and altered brainwave activity (altered EEG) are also reported in the scientific literature [94–107]. Biophysical mechanisms that may account for such effects can be found in various articles and reviews [136–144].

The public health implications of emerging wireless technologies are enormous because there has been a very rapid global deployment of both old and new forms in the last 15 years. In the United States, the deployment of wireless infrastructure has accelerated greatly in the last few years with 220,500 cell sites in 2008 [14–16]. Eighty-four percent of the population of the US own cell phones [16]. Annualized wireless revenues in 2008 will reach $144 billion and US spending on wireless communications will reach $212 billion by 2008. Based on the current 15% annual growth rate enjoyed by the wireless industry, in the next 5 years wireless will become a larger sector of the US economy than both the agriculture and automobile sectors. The annualized use of cell phones in the US is estimated to be 2.23 trillion minutes in 2008 [16]. There are 2.2 billion users of cell phones worldwide in 2008 [17] and many million more users of cordless phones.

Over 75 billion text messages were sent in the United States, compared with 7.2 billion in June 2005, according to

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CTIA, the Wireless Association, the leading industry trade group [16]. The consumer research company Nielsen Mobile, which tracked 50,000 individual customer accounts in the second quarter of this year, found that Americans each sent or received 357 text messages a month then, compared with 204 phone calls. That was the second consecutive quarter in which mobile texting significantly surpassed the number of voice calls [17].

The Electronics Industries Alliance (EIA) represents 80% of the $550 billion US electronics industry "that provides two million jobs for American workers." Its members include companies from the consumer electronics and telecommunications industries, among others [17].

There is intense industry competition for market share. Telecom taxes form an immense revenue generator for the government sector. Sale of the airwaves (auctions selling off wireless bandwidth) is a multi-million dollar industry for governments, and multi-billion dollar global advertising budgets are common. Lobbying dollars from the telecom-related industries are estimated to be $300 million annually. The media is nearly silent on health issues, perhaps in part because of global advertising revenues that compromise journalistic independence and discourage balanced coverage of health, equity and economic issues.

2. Evidence supporting a public health risk

Even if there is only a small risk to health from chronic use of and exposure to wireless technologies, there is the potential for a profound public health impact. RF radiation now saturates the airwaves, resulting in exposure to both users and non-users. The effects are both short-term (sleep disruption, hormone disruption, impairment of cognitive function, concentration, attention, behavior, and well-being) and they are almost certainly long-term (generational impacts on health secondary to DNA damage, physiological stress, altered immune function, electrosensitivity, miscarriage risks, effects on sperm quality and motility leading to infertiility, increased rates of cancer, and neurological diseases including Alzheimer's disease and ALS—at least for ELF exposures). (Chapters 5–12 of the BioInitiative Report [1] and papers in this Supplement.)

There is credible scientific evidence that RF exposures cause changes in cell membrane function, metabolism and cellular signal communication, as well as activation of proto-oncogenes and triggering of the production of stress proteins at exposure levels below current regulatory limits. There is also generation of reactive oxygen species, which cause DNA damage, chromosomal aberrations and nerve cell death. A number of different effects on the central nervous system have also been documented, including activation of the endogenous opioid systems, changes in brain function including memory loss, slowed learning, motor dysfunction and performance impairment in children, and increased frequency of headaches, fatigue and sleep disorders. Melatonin secretion is reduced, resulting in altered circadian rhythms and disruption of several physiological functions. (Chapters 5–12 of the BioInitiative Report [1] and papers in this Supplement.)

These effects can reasonably be presumed to result in adverse health effects and disease with chronic and uncontrolled exposures, and children may be particularly vulnerable [1,19]. The young are also largely unable to remove themselves from such environments. Second-hand non-ionizing radiation, like second-hand smoke may be considered of public health concern based on the evidence at hand.

2.1. Malignant brain tumors

At present, the most persuasive evidence for cancer resulting from RF exposure is that there is a significantly increased risk of malignant glioma in individuals that have used a mobile phone for 10 or more years, with the risk being elevated only on the side of the head on which the phone is used regularly (ipsilateral use) [1,3,4,6–8,18]. While the risk for adults after 10 or more years of use is reported to be more than doubled, there is some evidence beginning to appear that indicates that the risk is greater if the individual begins to use a mobile phone at younger ages. Hardell et al. [18] reported higher odds ratios in the 20–29-year-old group than other age ranges after more than 5 years of use of either analog or cordless phones. Recently in a London symposium Hardell reported that after even just 1 or more years of use there is a 5.2-fold elevated risk in children who begin use of mobile phones before the age of 20 years, whereas for all ages the odds ratio was 1.4. Studies from Israel have found that the risk of parotid gland tumors (a salivary gland in the cheek) is increased with heavy cell phone use [7]. The risk of acoustic neuroma (a benign but space-occupying tumor on the auditory nerve) is also significantly increased on the ipsilateral side of the head after 10 or more years of mobile phone use [1,3]. This relationship has also been documented in some of the published reports of the WHO Interphone Study, a decade-long 13-country international assessment of cell phone risks and cancer [6,8].

Kundi reports that "(E)pidemiological evidence compiled in the last 10 years starts to indicate an increased risk, in particular for brain tumors (glioma, meningioma, acoustic neuroma), from mobile phone use. Considering biases that may have been operating in most studies the risk estimates are rather too low, although recall bias could have increased risk estimates. The net result, when considering the different errors and their impact is still an elevated risk" [19].

The latency for most brain tumors is 20 years or more when related to other environmental agents, for example, to X-ray exposure. Yet, for cell phone use the increased risks are occurring much sooner than twenty years, as early as 10 years for brain tumors in adults and with even shorter latencies in children. This suggests that we may currently be significantly underestimating the impact of current levels of

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use of RF technology, since we do not know how long the average latency period really is. If it is 20 years, then the risk rate will likely be much higher than an overall doubling of risk for cell phone users if the peak comes later than 10 years. It may also signal very troubling risks for those who start using cell phones, and perhaps all wireless devices, in early childhood. We may not have proof of effect for decades until many hundreds of thousands of new cases of malignant gliomas are set in motion by long-term cell phone use.

The preliminary evidence that mobile phone use at younger ages may lead to greater risk than for older persons is of particular concern. There is a large body of evidence that childhood exposure to environmental agents poses greater risk to health than comparable exposure during adulthood [20,21]. There is reason to expect that children would be more susceptible to the effects of EMF exposure since they are growing, their rate of cellular activity and division is more rapid, and they may be more at risk for DNA damage and subsequent cancers. Growth and development of the central nervous system is still occurring well into the teenage years so that neurological changes may be of great importance to normal development, cognition, learning, and behavior.

A greater vulnerability of children to developing brain cancer from mobile phone use may be the consequence of a combination of patterns of use, stage of development and physical characteristics related to exposure. In addition to the fact that the brain continues to develop through the teen years, many young children and teenagers now spend very large periods of time using mobile phones. The brain is the main target organ of cell phones and cordless phones, with highest exposure to the same side as the phone is used. Further, due to anatomical reasons, the brain of a child is more exposed to RF radiation than the brain of an adult [22,23]. This is caused by the smaller brain size, a thinner pinna of the ear, thinner skin and thinner skull bone permitting deeper penetration into the child's brain. A recent French study showed that children absorb twice the RF from cell phone use as do adults [24].

In addition to concerns about cancer, there is evidence for short-term effects of RF exposure on cognition, memory and learning, behavior, reaction time, attention and concentration, altered brainwave activity (altered EEG) [95–108], and all of these effects argue for extreme caution with regard to exposure of children. The development of children into adults is characterized by faster cell division during growth, the long period needed to fully develop and mature all organ systems, and the need for properly synchronized neural development until early adulthood. Chronic, cumulative RF exposures may alter the normal growth and development of children and adversely affect their development and capacity for normal learning, nervous system development, behavior and judgment [1,97,102].

Prenatal exposure to EMF has been identified as a possible risk factor for childhood leukemia (1). Maternal use of cell phones has been reported to adversely affect fetal brain development, resulting in behavioral problems in those children by the time they reach school age [25]. Their exposure is involuntary in all cases. Children are largely unable to remove themselves from exposures to harmful substances in their environments.

2.2. *Plausible biological mechanisms for a relationship between RF exposure and cancer*

2.2.1. *DNA damage and oxidative stress*

Damage to DNA from ELF and from RF cell phone frequencies at very low intensities (far below FCC and ICNIRP safety limits) has been demonstrated in many studies [1,2,26–35]. Both single- and double-strand DNA damage have been reported by various researchers in different laboratories. This is damage to the human genome, and can lead to mutations which can be inherited, or which can cause cancer, or both.

Non-ionizing radiation is assumed to be of too low energy to cause direct DNA damage. However both ELF and RF radiation induce reactive oxygen species, free radicals that react with cellular molecules including DNA. Free-radical production and/or the failure to repair DNA damage (secondary to damage to the enzymes that repair damage) created by such exposures can lead to mutations. Whether it is greater free-radical production, reduction in anti-oxidant protection or reduced repair capacity, the result will be altered DNA, increased risk of cancer, impaired or delayed healing, and premature aging [36–54]. Exposures have also been linked to decreased melatonin production, which is a plausible biological mechanism for decreased cancer surveillance in the body, and increased cancer risk [34,39,44,46,47,49,50,54]. An increased risk of cancers and a decrease in survival has been reported in numerous studies of ELF and RF [55–69].

2.2.2. *Stress proteins (heat shock proteins or HSP)*

Another well-documented effect of exposure to low-intensity ELF and RF is the creation of stress proteins (heat shock proteins) that signal a cell is being placed under physiological stress) [70–80]. The HSP response is generally associated with heat shock, exposure to toxic chemicals and heavy metals, and other environmental insults. HSP is a signal of cells in distress. Plants, animals and bacteria all produce stress proteins to survive environmental stressors like high temperatures, lack of oxygen, heavy metal poisoning, and oxidative stress.

We can now add ELF and RF exposures to this list of environmental stressors that cause a physiological stress response. Very low-level ELF and RF exposures can cause cells to produce stress proteins, meaning that the cell recognizes ELF and RF exposures as harmful. This is another important way in which scientists have documented that ELF and RF exposures can be harmful, and it happens at levels far below the existing public safety standards. An additional concern is that if the stress goes on too long, the protective effect is diminished. The reduced response with prolonged exposure means the cell is less protected against

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damage, and this is why prolonged or chronic exposures may be harmful, even at very low intensities.

2.2.3. RF-induced gene expression changes

Many environment agents cause diseases, including cancer, not by direct damage to DNA but rather by up- or down-regulation of genes that regulate cell growth and function. Usually there are many genes whose expression is changed, and it is difficult to determine the exact changes responsible for the disease. Both ELF and RF exposures have been shown to result in altered gene expression. Olivares-Banuelos et al. [81] found that ELF exposure of chromaffin cells resulted in changed expression of 53 transcripts. Zhao et al. [82] investigated the gene expression profile of rat neurons exposed to 1800 MHz RF fields (2 W/kg) and found 24 up-regulated genes and 10 down-regulated genes after a 24-h exposure. The altered genes were involved in multiple cellular functions including cytoskeleton, signal transduction pathways and metabolism. Kariene et al. [83] exposed human skin to mobile phone radiation, and found by punch biopsy that 8 proteins were significantly altered in expression, consistent with gene induction. Several other studies have found altered gene expression following RF exposure, although none have been found that explain specific disease states [84].

DNA activation at very low ELF and RF levels, as in the stress response, and DNA damage (strand breaks and micronuclei) at higher levels, are molecular precursors to changes that are believed to lead to cancer. These, along with gene induction, provide plausible biological mechanisms linking exposure to cancer.

The biochemical pathways that are activated are the same for ELF and for RF exposures, and are non-thermal (do not require heating or induced electrical currents). This is true for the stress response, DNA damage, generation of reactive oxygen species as well as gene induction. Thus it is not surprising that the major cancers resulting from exposure to ELF and RF are the same, namely leukemia and brain cancer. The safety standards for both ELF and RF, based on protection from heating, are irrelevant and not protective. ELF exposure levels of only 5–10 mG have been shown to activate the stress response genes (http://www.bioinitiative.org, Sections 1 and 7 [1]).

3. Sleep, cognitive function and performance

The relationship of good sleep to cognition, performance and healing is well recognized. Sleep is a profoundly important factor in proper healing, anti-inflammatory benefits, reduction in physical symptoms of such as tendonitis, over-use syndrome, fatigue-induced lethargy, cognition and learning. Incomplete or slowed physiological recovery is common when sleep is impaired. Circadian rhythms that normalize stress hormone production (cortisol, for example) depend on synchronized sleep patterns.

People who are chronically exposed to low-level wireless antenna emissions report symptoms such as problems in sleeping (insomnia), as well as other symptoms that include fatigue, headache, dizziness, grogginess, lack of concentration, memory problems, ringing in the ears (tinnitus), problems with balance and orientation, and difficulty in multi-tasking [85–93,99]. In children, exposures to cell phone radiation have resulted in changes in brain oscillatory activity during some memory tasks [97,102]. Cognitive impairment, loss of mental concentration, distraction, speeded mental function but lowered accuracy, impaired judgment, delayed reaction time, spatial disorientation, dizziness, fatigue, headache, slower motor skills and reduced learning ability in children and adults have all been reported [85–108].

These symptoms are more common among "electrosensitive" individuals, although electrosensitivity has not been documented in double-blind tests of individual identifying themselves as being electrosensitive as compared to controls [109,110]. However people traveling to laboratories for testing are pre-exposed to a multitude of RF and ELF exposures, so they may already be symptomatic prior to actual testing. There is also evidence that RF exposures testing behavioral changes show delayed results; effects are observed after termination of RF exposure. This suggests a persistent change in the nervous system that may be evident only after time has passed, so is not observed during a short testing period.

3.1. Plausible biological mechanisms for neurobehavioral effects

3.1.1. The melatonin hypothesis

While there remains controversy as to the degree that RF and ELF fields alter neurobehavioral function, emerging evidence provides a plausible mechanism for both effects on sleep and cognition. Sleep is controlled by the central circadian oscillator in the suprachiasmatic nucleus, located in the hypothalamus. The activity of this central circadian oscillator is, in turn, controlled by the hormone, melatonin, which is released from the pineal gland [111]. There is considerable evidence that ELF exposure reduces the release of melatonin from the pineal gland—see Section 12 of the Bioinitiative Report [1]. There has been less study of the effects of RF exposure on melatonin release, but investigations have demonstrated a reduced excretion of the urinary metabolite of melatonin among persons using a mobile phone for more than 25 min per day [112]. In a study of women living near to radio and television transmitters, Clark et al. [113] found no effect on urinary melatonin metabolite excretion among pre-menopausal women, but a strong effect in post-menopausal women.

The "melatonin hypothesis" also provides a possible basis for other reported effects of EMFs. Melatonin has important actions on learning and memory, and inhibits electrophysiological components of learning in some but not all areas of the brain [114,115]. Melatonin has properties as a free-radical scavenger and anti-oxidant [116], and consequently,

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a reduction in melatonin levels would be expected to increase susceptibility to cancer and cellular damage. Melatonin could also be the key to understanding the relationship between EMF exposure and Alzheimer's disease. Noonan et al. [117] reported that there was an inverse relationship between excretion of the melatonin metabolite and the 1–42 amino acid form of amyloid beta in electric utility workers. This form of amyloid beta has been found to be elevated in Alzheimer's patients.

3.1.2. Blood–brain barrier alterations

Central nervous system effects of EMFs may also be secondary to damage to the blood–brain barrier (BBB). The blood–brain barrier is a critical structure that prevents toxins and other large molecules that are in peripheral blood from having access to the brain matter itself. Salford et al. [118] have reported that a 2-h exposure of rats to GSM-900 radiation with a SAR of 2–200 mW/kg resulted in nerve cell damage. In a follow-up study, Eberhardt et al. report that 2-h exposures to cell phone GSM microwave RF resulted in leakage of albumin across the blood–brain barrier and neuronal death [119]. Neuronal albumin uptake was significantly correlated to occurrence of damaged neurons when measured at 28 days post-exposure. The lowest exposure level was 0.12 mW/kg (0.00012 W/kg) for 2 h. The highest exposure level was 120 mW/kg (0.12 W/kg). The weakest exposure level showed the greatest effect in opening the BBB [118]. Earlier blood–brain studies by Salford and Schirmacher [120,121] report similar effects.

4. What are sources of wireless radiation?

There are many overlapping sources of radiofrequency and microwave emissions in daily life, both from industrial sources (like cell towers) and from personal items [cell and cordless phones, personal digital assistants (PDAs), wireless routers, etc.]. Published data on typical levels found in some cities and from some sources are available at http://www.bioinitiative.org [1,122–124].

Cell phones are the single most important source of radiofrequency radiation to which we are exposed because of the relatively high exposure that results from the phone being held right against the head. Cell phones produce two types of emissions that should be considered. First, the radiofrequency radiation (typically microwave frequency radiation) is present. However, there is also the contribution of the switching battery pack that produces very high levels of extremely low frequency electromagnetic field [125–127].

Cordless telephones have not been widely recognized as similar in emissions to cell phones, but they can and do produce significant RF exposures. Since people tend to use them as substitutes for in-home and in-office corded or traditional telephones, they are often used for long periods of time. As the range of cordless phones has increased (the distance away that you can carry on a conversation is related to the power output of the phone), the more powerful the RF signal will be. Hence, newer cordless phones may in some cases be similar to the power output of cell phones. The cumulative emissions from cell and cordless phones taken together should be recognized when considering the relative risks of wireless communication exposures.

PDAs such as the BlackBerry, Treo and iPhone units are 'souped-up' versions of the original voice communication devices (cell phones). The often produce far higher ELF emissions than do cell phones because they use energy from the battery very intensively for powering color displays and during data transmission functions (email, sending and receiving large files, photos, etc.) [125–127]. ELF emissions have been reported from PDAs at several tens to several hundreds of milligauss. Evidence of significantly elevated ELF fields during normal use of the PDA has public health relevance and has been reported in at least three scientific papers [125,128,129]. In the context of repetitive, chronic exposure to significantly elevated ELF pulses from PDAs worn on the body, relevant health studies point to a possible relationship between ELF exposure and cancer and pregnancy outcomes [130–133].

We include discussion of the ELF literature for two reasons. As mentioned above ELF activates the same biology as RF, it contributes to the total EMF burden of the body. In addition, PDAs and cell phones emit both radiofrequency/microwave radiation (RF) and extremely low frequency ELF from the battery switching of the device (the power source). Studies show that some devices produce excessively high ELF exposures during voice and data transmission. ELF is already classified as a 2B (Possible) Carcinogen by IARC, which means that ELF is indisputably an issue to consider in the wireless technology debate. ELF has been classified as a Group 2B carcinogen for all humans, not just children. The strongest evidence came from epidemiological studies on childhood leukemia, but the designation applies to all humans, both adults and children [1,25].

Wireless headsets that allow for conversations with cell phones at a distance from the head itself reduce the emissions. Depending on the type of wireless device, they may operate (transmit signal) only during conversations or they may be operational continuously. The cumulative dose of wireless headsets has not been well characterized under either form of use. Substantial cumulative RF exposure would be expected if the user wears a wireless headset that transmits a signal continuously during the day. However a critical factor is where the cell phone is placed. If worn on a belt with a headset, the exposure to the brain is reduced but the exposure to the pelvis may be significant.

Cell towers (called "masts" in Europe and Scandinavian countries) are wireless antenna facilities that transmit the cell phone signals within communities. They are another major source of RF exposures for the public. They differ from RF exposures from wireless devices like cell phones in that they produce much lower RF levels (generally 0.05 to 1–2 μW/cm^2 in the first several hundred feet around them) in comparison to several hundred microwatts per centimeter

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squared for a cell phone held at the head. However they create a constant zone of elevated RF for up to 24 h per day. many hours per day, and the exposure is whole body rather than localized at the head. These facilities are the distribution system for wireless voice communications, internet connections and data transmission within communities. They are often erected on free-standing towers. They may be constructed on telephone poles or electrical poles. They may be built into the façade or rooftops of buildings behind wood screening. These are called stealth installations for wireless antenna facilities. Some installations are camouflaged to resemble 'false trees or rocks'. They emit RF to provide cell service to specific "cells" or locations that receive the signal.

Other forms of wireless transmission that are common in areas providing cell service are wireless land area networks (WLAN), (WiMAX) and WIFI networks. Some cities are installing city-wide WIFI service to allow any user on the street to log into the internet (without cables or wire connections). WIFI installations may have a signal reach for a few hundred feet where WiMAX installations may transmit signal more than 10 miles, so produce a stronger RF emission for those in close proximity. Each type has its particular signal strength and intended coverage area, but what they have in common is the production of continuous RF exposure for those within the area. We do not know what the cumulative exposure (dose) might be for people living, working or going to school in continuously elevated RF fields, nor are the possible health implications yet known. However, based on studies of populations near cell sites in general, there is a constellation of generally observed health symptoms that are reported to occur [85–107]. In this regard it is important to note that children living near to AM radio transmitters have been found to elevated risks of leukemia [134,135]. While AM radio RF fields are lower in frequency than that common in mobile phones, this is a total body irradiation with RF. The fact that leukemia, not brain cancer, is apparent in these studies suggests that leukemia is the cancer seen at the lowest levels of both ELF and RF fields under the circumstances of whole-body exposure.

Commercial surveillance systems or security gates pose an additional source of strong RF exposures. They are ubiquitous in department stores, markets and shops at the entry and exit points to discourage shoplifting and theft of goods. Security gates can produce excessively high RF exposures (although transitory) and have been associated with interference with pacemakers in heart patients. The exposure levels may approach thermal public safety limits in intensity, although no one expects a person to stand between the security gate bars for more than 6 min (safety limits for uncontrolled public access are variable depending on the frequency, but are all averaged over a 6-min exposure period).

RFID chips (radiofrequency identification chips) are being widely used to track purchases and for security of pets, and in some cases to keep track of patients with Alzheimer's disease and of children. RFID chips are implanted in fabrics, inserted in many types of commercial goods, and can be implanted under the skin. They create a detectable signal to track the location of people and goods.

5. Problems with existing public health standards (safety limits)

If the existing standards were adequate none of the effects documented above should occur at levels to which people are regularly exposed. The fact that these effects are seen with our current ambient levels of exposure means that our existing public safety standards are obsolete. It also means that new, biologically based public exposure standards for wireless technologies are urgently needed. Whether it is feasible to achieve low enough levels that still work and also protect health against effects of chronic RF exposure – for all age groups – is uncertain. Whether we can protect the public and still allow the kinds of wireless technology uses we see today is unknown.

The nature of electromagnetic field interactions with biological systems has been well studied [136–144]. For purposes of standard-setting processes for both ELF and RF, the hypothesis that tissue damage can result only from heating is the fundamental flaw in the misguided efforts to understand the basic biological mechanisms leading to health effects.

The thermal standard is clearly untenable as a measure of dose when EMF stimuli that differ by many orders of magnitude in energy can stimulate the same biological response. In the ELF range, the same biological changes occur as in the RF, and no change in temperature can even be detected. With DNA interactions the same biological responses are stimulated in ELF and RF ranges even though the frequencies of the stimuli differ by many orders of magnitude. The effects of EMF on DNA to initiate the stress response or to cause molecular damage reflect the same biology in different frequency ranges. For this reason it should be possible to develop a scale based on DNA biology, and use it to define EMF dose in different parts of the EM spectrum. We also see a continuous scale in DNA experiments that focus on molecular damage where single and double strand breaks have long been known to occur in the ionizing range, and recent studies have shown similar effects in both ELF and RF ranges [144].

Existing standard-setting bodies that regulate wireless technologies, assume that there are no bioeffects of concern at exposure levels that do not cause measurable heating. However, it has been established beyond any reasonable doubt that bioeffects and some adverse health effects occur at far lower levels of RF and ELF exposure where no heating (or induced current) occurs; some effects are shown to occur a thousand times or more below the existing public safety limits. New, biologically based public exposure limits are urgently needed. New wireless technologies for cell and cordless phones, other wireless communication and data transmission systems affect living organisms in new ways that our antiquated safety limits have not foreseen, nor protected against.

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The exposure of children to electromagnetic fields has not been studied extensively; in fact, the Federal Communications Commission (FCC) standards for exposure to radiofrequency radiation are based on the height, weight and stature of a 6-foot tall man, not scaled to children or adults of smaller stature. They do not take into account the unique susceptibility of growing children to exposures, nor are there studies of particular relevance to children.

In addition there is a problem in the consideration of the level of evidence taken into consideration by these bodies. There have not been adequate animal models shown to have cancer as an endpoint, and a perception that no single mechanism is proven to explain these associations. Thus these committees have tended to ignore or minimize the evidence for direct hazard to humans, and believe there is no proof of cause and effect. These bodies assume from the beginning that only conclusive scientific evidence (absolute proof) will be sufficient to warrant change, and refuse to take action on the basis of a growing body of evidence which provides early but consequential warning of risks.

The Radiofrequency Interagency Working Group of the US governmental agencies involved in RF matters (RFIAWG) issued a Guidelines Statement in June of 1999 that concluded the present RF standard "may not adequately protect the public" [145]. The RFIAWG identified fourteen (14) issues that they believe are needed in the planned revisions of ANSI/IEEE RF exposure guidelines including "to provide a strong and credible rationale to support RF exposure guidelines". In particular, the RFIAWG criticized the existing standards as not taking into account chronic, as opposed to acute exposures, modulated or pulsed radiation (digital or pulsed RF is proposed at this site), time-averaged measurements that may erase the unique characteristics of an intensity-modulated RF radiation that may be responsible for reported biologic effects, and stated the need for a comprehensive review of long-term, low-level exposure studies, neurological-behavioral effects and micronucleus assay studies (showing genetic damage from low-level RF) [145]. This important document from relevant US agencies questions existing standards in the following ways: (a) selection of an adverse effect level for chronic exposures not based on tissue heating and considering modulation effects; (b) recognition of different safety criteria for acute and chronic exposures at non-thermal or low-intensity levels; (c) recognition of deficiencies in using time-averaged measurements of RF that does not differentiate between intensity-modulated RF and continuous wave (CW) exposure, and *therefore may not adequately protect the public*; (d) having standards based on adult males rather than considering children to be the most vulnerable group.

6. Prudent public health responses

Emerging environmental health problems require preventative public health responses even where scientific and medical uncertainties still exist, but where policy decisions today may greatly reduce human disease and societal costs tomorrow.

Policy decisions in public health must address some amount of uncertainty when balancing likely benefits and estimated costs. Although new insight will allow better appreciation of difficult issues, such as those occurring in environmental and occupational health, an expanded perspective may also enlarge the list of problems that need to be managed. Ignoring the problems carries its own costs (as deferring a decision is a decision in itself). With environmental and other public health problems becoming increasingly complex and international in scope, scientific documentation alone rarely justifies simple solutions [146].

Social issues regarding the controversy over public and occupational exposures to ELF and RF center on the resolute adherence to existing ICNIRP and FCC/IEEE standards by many countries, in the face of growing scientific evidence of health risks at far lower levels [10]. The composition of these committees, usually with excessive representation of the physics and engineering communities rather than public health professionals, results in a refusal to adopt biologically based exposure standards. Furthermore, there is widespread belief that governments are ignoring this evidence and there is widespread distrust of and lack of confidence in governments and their health agencies. The basis on which most review bodies and standard-setting agencies have avoided the conclusion that the science is strong enough to warrant new safety limits for ELF and RF is to require a demonstration of absolute proof before taking action. A causal level of evidence, or scientific certainty standard is implicit in nearly all reviews of the ELF and RF science, although this runs counter to good public health protection policies.

There is no question that global implementation of the safety standards proposed in the Bioinitiative Report, if implemented abruptly and without careful planning, have the potential to not only be very expensive but also disruptive of life and the economy as we know it. Action must be a balance of risk to cost to benefit. The major risk from maintaining the status quo is an increasing number of cancer cases, especially in young people, as well as neurobehavioral problems at increasing frequencies. The benefits of the status quo are expansion and continued development of communication technologies. But we suspect that the true costs of even existing technologies will only become much more apparent with time. Whether the costs of remedial action are worth the societal benefits is a formula that should reward precautionary behavior. Prudent corporate policies should be expected to address and avoid future risks and liabilities, otherwise, there is no market incentive to produce safe (and safer) products.

The deployment of new technologies is running ahead of any reasonable estimation of possible health impacts and estimates of probabilities, let alone a solid assessment of risk. However, what has been missing with regard to EMF has been an acknowledgement of the risk that is demonstrated by

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the scientific studies. There is clear evidence of risk, although the magnitude of the risk is uncertain, and the magnitude of doing nothing on the health effects cost to society is similarly uncertain. This situation is very similar to our history of dealing with the hazards of smoking decades ago, where the power of the industry to influence governments and even conflicts of interest within the public health community delayed action for more than a generation, with consequent loss of life and enormous extra health care costs to society. New standards are warranted now, based on the totality of scientific evidence; the risks of taking no-action, the large population at risk, costs associated with ignoring the problem in new and upgraded site selection and construction, and the loss of public trust by ignoring the problem.

Direct medical and rehabilitative health costs associated with treatment for diseases that are reasonably related to wireless technologies may be very large. Although there is uncertainty involved in how much disease is related to wireless exposures, the mere scale of the problem with several billion users of cell phones and even larger impacts on bystander populations (from cell site exposures, from other WI-FI and wireless exposures in-home and commercial use, etc.) the associated public health costs will likely be monumental. Furthermore the costs to families with cancers, neurological diseases or learning disabilities in children related in part or in whole to wireless technologies extend beyond medical costs. They may reasonably extend to family disruption and family psychological problems, losses in job productivity and income loss.

The history of governments and their official health agencies to deal with emerging and newly identified risks to health is not good [147–149]. This is particularly true where industry investments in new products and technologies occur without full recognition, disclosure or even knowledge of possible health consequences. Large economic investments in polluting industries often make for perilously slow regulatory action, and the public health consequences may be very great as a result [150,151].

Free markets do not internalize the costs to society of "guessing wrong". Unexpected or hidden health costs of new technologies may not be seen for many years, when the ability to recall or to identify the precise exposures related to disease outcomes is difficult or impossible. The penalty nearly always falls to the individual, the family or the taxpayer and not to the industry that benefits economically—at least in free-market economies. Thus, the profits go to industry but the costs may go to the individual who can suffer both diminished quality of life and health and economic disadvantage. If all disease endpoints that may be reasonably related to chronic exposure to electromagnetic fields are considered even a small attributable fraction for one or more industries, it will have enormous global impact on public health. The public health implications are immense. But they can be reduced by strong government and public health interventions providing information on alternatives to wireless technologies, public education campaigns, health advisories, requirements for redesign of wireless devices, proscription of use of wireless devices by children and teenagers, strong and independent research programs on causes and prevention of EMF-related diseases, and consultation with all stakeholders on issues relating to involuntary exposures (bystander or second-hand radiation exposures from wireless technologies) (Table 1).

Table 1
Public health implications of wireless technologies argue for change in governmental and health agency actions.

Secure US and EU legislative mandates for safer technologies for communication and data transmission, for security and surveillance needs.
Promote wired alternatives for voice and data communication (cable, fiber-optic)
Discourage or ban use of cell phones by children and young teen-agers
Provide permanent (unremovable) labels on cell phones "Not for use by children under the age of 16"
Implement national public education campaigns on health issues (cell phones, cordless phones, PDAs, wireless internet, city-wide WI-FI, WLAN and WiMAX exposures
Promote industry redesign for safer products: support innovation for alternatives and solutions
Slow or stop deployment of wireless technologies to discourage reliance on wireless technologies for communication and security needs
Put the burden of proof on industry to show "new wireless tech" is safe before deployment
Adopt and enforce restricted use areas for sensitive or more vulnerable segments of society including low-EMF environments in public areas and "No Cell" zones in airports, hospitals, schools
Acknowledge FCC and ICNIRP thermal safety standards are obsolete for wireless technologies
Appoint new standard-setting bodies familiar with biological effects to develop new guidelines for public safety limits.
Develop new biologically based standards that address low-intensity, chronic exposures
Require standard of evidence and level of proof = public health
Reject "causal" standard of evidence for taking action on science
Make industry financially liable for "guessing wrong" and ignoring health risks

The scientific information contained in this Supplement argues for thresholds or guidelines that are substantially below current FCC and ICNIRP standards for localized exposures to wireless devices and for whole-body exposure. Uncertainty about how low such standards might have to go to be prudent from a public health standpoint should not prevent reasonable efforts to respond to the information at hand. No lower limit for bioeffects and adverse health effects from RF has been established, so the possible health risks of wireless WLAN and WI-FI systems, for example, will require further research. No assertion of safety at any level of wireless exposure (chronic exposure) can be made at this time. The lower limit for reported human health effects has dropped 100-fold below the safety standard (for mobile phones and PDAs); 1000–10,000-fold for other wireless (cell towers at distance; WI-FI and WLAN devices). The entire basis for safety standards is called into question, and it is not unreasonable to question the safety of RF at any level.

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It is likely that for both ELF and RF, as for other carcinogens, there is no threshold of exposure that is without risk, but the magnitude of the risk increases linearly with the level of exposure. Our society will not go back to the pre-electric and pre-wireless age, but the clear evidence of health hazards to the human population from exposure mandates that we develop ways in which to reduce exposure through education, new technologies and the establishment of biomedically based standards.

7. Conclusions and recommended actions

New ELF limits are warranted based on a public health analysis of the overall existing scientific evidence. These limits should reflect environmental levels of ELF that have been demonstrated to increase risk for childhood leukemia, and possibly other cancers and neurological diseases. ELF limits should be set below those exposure levels that have been linked in childhood leukemia studies to increased risk of disease, plus an additional safety factor. It is no longer acceptable to build new power lines and electrical facilities that place people in ELF environments that have been determined to be risky. These levels are in the 2–4 milligauss (mG) range (0.2–0.4 μT), not in the 10 s of mG or 100 s of mG. The existing ICNIRP limit is 1000 mG (100 μT) and 904 mG (90.4 μT) in the US for ELF is outdated and based on faulty assumptions. These limits are can no longer be said to be protective of public health and they should be replaced. A safety buffer or safety factor should also be applied to a new, biologically based ELF limit, and the conventional approach is to add a safety factor lower than the risk level.

While new ELF limits are being developed and implemented, a reasonable approach would be a 1 mG (0.1 μT) planning limit for habitable space adjacent to all new or upgraded power lines and a 2 mG (0.2 μT) limit for all other new construction. It is also recommended that a 1 mG (0.1 μT) limit be established for existing habitable space for children and/or women who are pregnant (because of the possible link between childhood leukemia and *in utero* exposure to ELF). This recommendation is based on the assumption that a higher burden of protection is required for children who cannot protect themselves, and who are at risk for childhood leukemia at rates that are traditionally high enough to trigger regulatory action. This situation in particular warrants extending the 1 mG (0.1 μT) limit to existing occupied space. "Establish" in this case probably means formal public advisories from relevant health agencies. While it is not realistic to reconstruct all existing electrical distribution systems, in the short-term; steps to reduce exposure from these existing systems need to be initiated, especially in places where children spend time, and should be encouraged. These limits should reflect the exposures that are commonly associated with increased risk of childhood leukemia (in the 2–5 mG (0.2–0.5 μT) range for all children, and over 1.4 mG (0.14 μT) for children age 6 and younger). Nearly all of the occupational studies for adult cancers and neurological diseases report their highest exposure category is 4 mG (0.4 μT) and above, so that new ELF limits should target the exposure ranges of interest, and not necessarily higher ranges.

Avoiding chronic ELF exposure in schools, homes and the workplace above levels associated with increased risk of disease will also avoid most of the possible bioactive parameters of ELF discussed in the relevant literature.

It is not prudent public health policy to wait any longer to adopt new public safety limits for ELF. These limits should reflect the exposures that are commonly associated with increased risk of childhood leukemia (in the 2–5 mG (0.2–0.5 μT) range for all children, and over 1.4 mG (0.14 μT) for children age 6 and younger). Avoiding chronic ELF exposure in schools, homes and the workplace above levels associated with increased risk of disease will also avoid most of the possible bioactive parameters of ELF discussed in the relevant literature.

The rapid deployment of new wireless technologies that chronically expose people to pulsed RF at levels reported to cause bioeffects, which in turn, could reasonably be presumed to lead to serious health impacts, is a public health concern. There is suggestive to strongly suggestive evidence that RF exposures may cause changes in cell membrane function, cell communication, metabolism, activation of proto-oncogenes and can trigger the production of stress proteins at exposure levels below current regulatory limits. Resulting effects can include DNA breaks and chromosome aberrations, cell death including death of brain neurons, increased free-radical production, activation of the endogenous opioid system, cell stress and premature aging, changes in brain function including memory loss, retarded learning, performance impairment in children, headaches and fatigue, sleep disorders, neurodegenerative conditions, reduction in melatonin secretion and cancers (BioInitiative Report Chapters 5–10, 12) [1].

This information now argues for thresholds or guidelines that are substantially below current FCC and ICNIPR standards for whole-body exposure. Uncertainty about how low such standards might have to go to be prudent from a public health standpoint should not prevent reasonable efforts to respond to the information at hand. No lower limit for bioeffects and adverse health effects from RF has been established, so the possible health risks of wireless WLAN and WI-FI systems, for example, will require further research and no assertion of safety at any level of wireless exposure (chronic exposure) can be made at this time. The lower limit for reported human health effects has dropped 100-fold below the safety standard (for mobile phones and PDAs); 1000–10,000-fold for other wireless (cell towers at distance; WI-FI and WLAN devices). The entire basis for safety standards is called into question, and it is not unreasonable to question the safety of RF at any level.

A cautionary target level for pulsed RF exposures for ambient wireless that could be applied to RF sources from cell tower antennas, WI-FI, WI-MAX and other similar sources

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is proposed. The recommended cautionary target level is 0.1 microwatts per centimeter squared ($\mu W/cm^2$) (or 0.614 V per meter or V/m) for pulsed RF where these exposures affect the general public; this advisory is proportionate to the evidence and in accord with prudent public health policy. A precautionary limit of 0.1 $\mu W/cm^2$ should be adopted for outdoor, cumulative RF exposure. This reflects the current RF science and prudent public health response that would reasonably be set for pulsed RF (ambient) exposures where people live, work and go to school. This level of RF is experienced as whole-body exposure, and can be a chronic exposure where there is wireless coverage present for voice and data transmission for cell phones, pagers and PDAs and other sources of radiofrequency radiation. An outdoor precautionary limit of 0.1 $\mu W/cm^2$ would mean an even lower exposure level inside buildings, perhaps as low as 0.01 $\mu W/cm^2$. Some studies and many anecdotal reports on ill health have been reported at lower levels than this; however, for the present time, it could prevent some of the most disproportionate burdens placed on the public nearest to such installations. Although this RF target level does not preclude further rollout of WI-FI technologies, we also recommend that wired alternatives to WI-FI be implemented, particularly in schools and libraries so that children are not subjected to elevated RF levels until more is understood about possible health impacts. This recommendation should be seen as an interim precautionary limit that is intended to guide preventative actions; and more conservative limits may be needed in the future.

Broadcast facilities that chronically expose nearby residents to elevated RF levels from AM, FM and television antenna transmission are also of public health concern given the potential for very high RF exposures near these facilities (antenna farms). RF levels can be in the 10 s to several 100 s of $\mu W/cm^2$ in residential areas within half a mile of some broadcast sites (for example, Lookout Mountain, Colorado and Awbrey Butte, Bend, Oregon). Like wireless communication facilities, RF emissions from broadcast facilities that are located in, or expose residential populations and schools to elevated levels of RF will very likely need to be re-evaluated for safety.

For emissions from wireless devices (cell phones, personal digital assistant or PDA devices, etc.) there is enough evidence for increased risk of brain tumors and acoustic neuromas now to warrant intervention with respect to their use. Redesign of cell phones and PDAs could prevent direct head and eye exposure, for example, by designing new units so that they work only with a wired headset or on speakerphone mode.

These effects can reasonably be presumed to result in adverse health effects and disease with chronic and uncontrolled exposures, and children may be particularly vulnerable. The young are also largely unable to remove themselves from such environments. Second-hand radiation, like second-hand smoke is an issue of public health concern based on the evidence at hand.

In summary, the following recommendations are made:

- ELF limits should be set below those exposure levels that have been linked in childhood leukemia studies to increased risk of disease, plus an additional safety factor. It is no longer acceptable to build new power lines and electrical facilities that place people in ELF environments that have been determined to be risky (at levels generally at 2 mG (0.2 μT) and above).
- While new ELF limits are being developed and implemented, a reasonable approach would be a 1 mG (0.1 μT) planning limit for habitable space adjacent to all new or upgraded power lines and a 2 mG (0.2 μT) limit for all other new construction, It is also recommended for that a 1 mG (0.1 μT) limit be established for existing habitable space for children and/or women who are pregnant. This recommendation is based on the assumption that a higher burden of protection is required for children who cannot protect themselves, and who are at risk for childhood leukemia at rates that are traditionally high enough to trigger regulatory action. This situation in particular warrants extending the 1 mG (0.1 μT) limit to existing occupied space. "Establish" in this case probably means formal public advisories from relevant health agencies.
- While it is not realistic to reconstruct all existing electrical distributions systems, in the short-term; steps to reduce exposure from these existing systems need to be initiated and should be encouraged, especially in places where children spend time.
- A precautionary limit of 0.1 $\mu W/cm^2$ (which is also 0.614 V per meter) should be adopted for outdoor, cumulative RF exposure. This reflects the current RF science and prudent public health response that would reasonably be set for pulsed RF (ambient) exposures where people live, work and go to school. This level of RF is experienced as whole-body exposure, and can be a chronic exposure where there is wireless coverage present for voice and data transmission for cell phones, pagers and PDAs and other sources of radiofrequency radiation. Some studies and many anecdotal reports on ill health have been reported at lower levels than this; however, for the present time, it could prevent some of the most disproportionate burdens placed on the public nearest to such installations. Although this RF target level does not preclude further rollout of WI-FI technologies, we also recommend that wired alternatives to WI-FI be implemented, particularly in schools and libraries so that children are not subjected to elevated RF levels until more is understood about possible health impacts. This recommendation should be seen as an interim precautionary limit that is intended to guide preventative actions; and more conservative limits may be needed in the future.

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